高金明典，早川善郎，入野田崇，他．
地域連携による胃癌治療―術後早期から終末期まで―．第83回日本胃癌学会．2011.3.5．三沢

研究成果の刊行に関する一覧表

今本治彦

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| M.Imano, H.Imamoto, T.Itoh, T.Satou, Y.F.Peng, A.Shinkai, M,Tsubaki, T.Yasua, S.Nishida, Y.Takeyama, K.Okuno, H.shiozaki | Impact of Intraperitoneal Chemotherapy after Gastrectomy with Positive Cytological Findings in Peritoneal Washings | Eur Surg Res | 47 | 254-259 | 2011 |
| .M.Imano, H.Imamoto, T.Itoh, T.Satou, Y.F.Peng, A.Yasuda, H.Kato, O.Shiraishi, M.Shinkai, T.Yasuda, Y.Takeyama, K.Okuno, H.Shiozaki | Safety of Intraperitoneal Administration of Paclitaxel After Gastrectomy With En-Bloc D2 Lymph Node Dissection | Jounal of Surgical Oncology | 5 | | 2011 |

藤原義之

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| Fujiwara Y, Takiguchi S, Nakajima K, Miyata H, Yamasaki M, Kurokawa Y, Mori M, and Doki Y | Intraperitoneal, docetaxel combined with S-1 for advanced gastric cancer with peritoneal dissemination | J Surg Oncol | 105 | 38-42 | 2012 |
| Fujiwara Y, Takiguchi S, Nakajima K, Miyata H, Yamasaki M, Kurokawa Y, Okada K, Mori M, Doki Y | Neoadjuvant Intraperitoneal and Systemic Chemotherapy for Gastric Cancer Patients with Peritoneal Dissemination | Ann Surg Oncol | 18 | 3726-31 | 2011 |

| | | | | | |
|---|---|---|---|---|---|
| Monn JH, Fujiwara Y, Nakamura Y, Okada K, Hanada H, Sakakura C, Takiguchi S, Nakajima K, Miyata H, Ya,masaki M, Kurokawa Y, Mori M, Doki Y | REGIV as a potential biomarker for peritoneal dissemination in gastric adenocarcinoma | J Surg Oncol | 105 | 189-94 | 2012 |
| 藤原義之、瀧口修司、黒川幸典、中島清一、宮田博志、山崎誠、森正樹、土岐祐一郎 | 腹膜播種を伴う胃癌に対する外科治療 | 消化器外科 | 34 | 545-551 | 2011 |
| 藤原義之 | 切除不能進行再発胃癌に対する新たな免疫化学療法の開発 | がん治療のあゆみ | 30 | 45-51 | 2011 |

肥田圭介

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| Koeda K Nishizuka S Wakabayasi G | Minimally invasive surgery for gastric cancer: the future standard of care | World J Surg | 35 | 1469-1477 | 2011 |
| 藤原久貴 肥田圭介 他 | PTX/CDDPを用いた化学放射線療法とS-1の投与によりCRが認められている食道胃接合部癌の1例 | 癌と化学療法 | 38(10) | 1683-1686 | 2011 |
| 御供真吾 肥田圭介 他 | S-1/CDDPが奏功した多発骨転移・遠隔リンパ節転移を伴った進行胃癌の1例 | 癌と化学療法 | 39(1) | 1683-1686 | 2011 |

野村栄治

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| 野村栄治、李相雄、徳原孝哉、辻求、谷川允彦 | 胃癌 | 臨床外科 | 66(4) | 420-425 | 2011 |
| 李相雄、野村栄治、徳原孝哉、横山和武、藤岡大也、谷川允彦 | 腹腔鏡下胃切除術の周術期管理 | 外科治療 | 104 (6月増刊号) | 588-593 | 2011 |
| E.Nomura, SW Lee, G Bouras, T.Tokuhara, M.Hayashi, M.Hiramatsu, J .Okuda N Tanigawa | Functional outcomes according to the size of the gastric remnant and type of reconstruction followinglaparoscopic distal gastrectomy for gastric cancer | Gastric Cancer | 14(3) | 279-284 | 2011 |

| | | | | | |
|---|---|---|---|---|---|
| G Bouras,<br>SW Lee,<br>E.Nomura,<br>T.Tokuhara,<br>S.Tsunemi,<br>N.Tanigawa | Comparative analysis of station-specific lymph node yield in laparoscopic and open distal gastrectomy for early gastric cancer | Surgical Laparoscopy Endoscopy &Percutaneo us Techniques | 21(6) | 424-428 | 2011 |
| SW Lee,<br>E.Nomura,<br>T.Tokuhara,<br>M.Kawai,<br>N.Matsuhashi,<br>K.Yokoyama,<br>H.Fujioka,<br>M.Hiramatsu,J Okuda,<br>K.Uchiyama | Laparoscopic Technique and Initial Experience with Knotless,Unidirectional Barbed Suture ClosureforStaple-Conserving,Delta-Shaped Gastroduodenostomy after Distal Gastrectomy | Journal of the American College of Surgeons | 13(6) | e39-45 | 2011 |

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# Impact of Intraperitoneal Chemotherapy after Gastrectomy with Positive Cytological Findings in Peritoneal Washings

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**Key Words**
Gastric cancer · Gastrectomy · Intraperitoneal chemotherapy

**Abstract**
***Background:*** There is no standard treatment available for gastric cancer patients whose sole 'non-curative factor' is positive cytological findings in peritoneal washings (CFPW). The aim of this study was to examine the safety, pharmacokinetics and efficacy for free intraperitoneal cancer cells of intraperitoneal chemotherapy with paclitaxel after gastrectomy with en bloc D2 lymph node dissection in cases of gastric cancer with positive CFPW. ***Methods:*** Ten patients with gastric cancer who underwent gastrectomy and systemic lymphadenectomy with D2 dissection, without any other non-curative factors besides positive CFPW, were treated with early postoperative intraperitoneal paclitaxel. Intra-chemotherapeutic toxicity and operative complications were measured using NCI-CTC version 3.0. Intraperitoneal and plasma paclitaxel concentrations were measured using a high-performance liquid chromatographic assay. ***Results:*** Grade 3/4 toxic effects included anemia (20%) and neutropenia (10%) that required no treatment. Operative complications were, for example, superficial surgical site infections (10%) that were treated with antibiotics. No viable cancer cells were observed in the intra-abdominal fluid 24 h after intraperitoneal administration of paclitaxel. The intraperitoneal/plasma area under the drug concentration-time curve ratio was 2,003.3:1. ***Conclusion:*** Intraperitoneal chemotherapy with paclitaxel is a safe and effective treatment modality for free intraperitoneal cancer cells.



## Introduction

Gastric cancer is a life-threatening disease with over 600,000 deaths per year worldwide [1]. Recent advances in the treatment of gastric cancer have improved clinical outcomes [2], but gastric cancer patients with peritoneal carcinomatosis (PC) still have a poor overall prognosis [3]. In Japan, even in the absence of PC, survival rates of patients with positive cytological findings in peritoneal washings (CFPW) were similar to those of patients with macroscopically evident PC [4]. Kodera et al. [5] reported

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that patients with positive CFPW had a greater risk of PC recurrence and, hence, a significantly worse prognosis. In Europe and in the United States, the prognostic significance of positive CFPW has also been acknowledged [6, 7]. Therefore, a new, more definitive treatment modality has been sought to improve survival in patients with positive CFPW.

There is no standard treatment for patients with positive CFPW. Paclitaxel has delayed clearance from the peritoneal cavity because of its high molecular weight and bulky structure, and the advantage of intraperitoneal exposure to paclitaxel has been demonstrated by high intraperitoneal/plasma ratios on examination of areas under the drug concentration-time curves (AUC) [8–11]. However, penetration of intraperitoneal chemotherapy (IPC) agents into the peritoneal surfaces is limited, and the effective diffusion distance into the tissues is reported to be in the order of 100 μm [12]. Therefore, patients with very small tumor volumes at the time of IPC may benefit more from this therapy. In brief, cases undergoing gastrectomy, without non-curative factors except for positive CFPW, might be good candidates for IPC.

The aim of this preliminary study was to examine the safety, efficacy for free intraperitoneal cancer cells, possible efficacy for survival and pharmacokinetics of IPC after gastrectomy with en bloc D2 lymph node dissection in cases with gastric cancer and positive CFPW.

## Patients and Methods

*Patient Selection*

We designed a preliminary prospective clinicopathological study. As the treatment group, we reviewed patients with gastric cancer and positive CFPW, initially diagnosed at laparotomy, who had undergone gastrectomy with systemic lymphadenectomy and D2 dissection in our department between 2004 and 2009.

Consequently, all patients met the following eligibility criteria that are frequently used in conventional clinical trials [13, 14]: (1) histologically proven gastric adenocarcinoma; (2) positive CFPW at laparotomy; (3) R1 resection by gastrectomy with systemic lymphadenectomy and D2 dissection; (4) adequate bone marrow function (leukocyte count 3,000–12,000 $mm^3$, neutrophil count ≥1,500/$mm^3$, and platelet count ≥100,000/$mm^3$); (5) adequate liver function (total serum bilirubin ≤1.5 mg/dl and serum transaminase levels more than two times the upper limit of normal); (6) adequate renal function (serum creatinine ≤1.5 mg/dl); (7) Eastern Clinical Oncology Group scale performance status 1 or less; (8) aged 20–75 years; (9) no other severe medical conditions or active malignancies, and (10) no previous chemotherapy. In addition, as a control group, we investigated gastric cancer patients with positive cytology alone, who did not undergo this treatment in our department between 1997 and 2000.

In accordance with the Kinki University Faculty of Medicine policy, written informed consent was obtained from the patients at operation. Patients predicted to be eligible were informed about the therapeutic strategy before surgery, emphasizing its potential benefits as well as the possible risk of mortality and morbidity, prior to operation. Finally, informed consent was given by all patients.

*Cytopathology*

Specimens for cytological examination were obtained at laparotomy, before manipulation of the tumor. Isotonic saline (100 ml) was instilled into the left subdiaphragmatic area and pelvis. After manual agitation, the washings were retrieved by aspiration. For cytological examination, the washings were centrifuged for 3 min, and direct smears were prepared and fixed in 95% ethanol. Two slides were prepared for each patient and stained using the Papanicolaou method. All slides were reviewed independently by two cytopathologists.

To investigate the efficacy of intraperitoneal paclitaxel administration, intra-abdominal fluid collected from the drainage tube inserted in the foramen of Winslow and/or in the left subdiaphragmatic area was examined 24 and 48 h after intraperitoneal administration of paclitaxel using the same methodology in all 9 patients who gave their informed consent.

*Gastrectomy with En Bloc D2 Lymph Node Dissection*

The surgical procedure was either total gastrectomy, for proximal tumors, or subtotal gastrectomy, where the primary tumor was located distally in the stomach with a 5-cm 'safe' margin. In all cases, an en bloc D2 lymph node dissection was performed according to the Japanese Gastric Cancer Association guidelines [15].

*Early Postoperative IPC*

For IPC, paclitaxel was administered at a dose of 80 mg/$m^2$ (which corresponds to the weekly intravenous dose of paclitaxel) [16]. In each patient, paclitaxel (dissolved in isotonic saline to a final volume of 1 liter) was instilled into the peritoneal cavity at the end of the operation through the almost completely closed incision. All drainage tubes within the abdominal cavity were clamped for 24 h after drug administration.

*Pharmacokinetic Analysis*

Pharmacokinetic studies were performed on 5 patients who gave their informed consent. Peritoneal samples from the drainage tube inserted in the foramen of Winslow and/or in the left subdiaphragmatic region and plasma samples were obtained during and 0.5, 1, 2, 3, 4, 6, 24 and 48 h after drug administration. Samples were collected in heparinized tubes and centrifuged, and the supernatant was stored at −20°C until required. Paclitaxel concentrations were measured using a high-performance liquid chromatography assay as previously described [17]. The AUC from 0–48 h in the peritoneal fluid (AUC peri, 0–48 h) and in plasma (AUC pla, 0–48 h) was estimated using the trapezoidal method.

The clinicopathological classifications were determined according to the criteria of the TNM Classification of Malignant

**Table 1.** Overall characteristics of 10 gastric cancer patients with positive CFPW

| Patient No. | Gender/ age, years | TNM stage | Borrmann type | Histological type | Type of resection | Operative complications | Adjuvant chemotherapy | Follow-up days | Current status |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M/56 | pT3, N2, M0 | 3 | diffuse | DG | none | S-1 (21 months) | 790 | alive, WR |
| 2 | F/66 | pT4a, N3a, M0 | 3 | intestinal | DG | none | W-PTX (2 months) | 792 | alive, WR |
| 3 | M/64 | pT3, N3a, M0 | 4 | diffuse | TG | none | S-1 (8 months | 688 | died, PC |
| 4 | M/73 | pT4a, N3b, M0 | 3 | intestinal | TG | none | nil | 1,151 | died, DLM |
| 5 | M/55 | pT4a, N3a, M0 | 3 | intestinal | TG | none | S-1 (48 months) | 1,742 | alive, WR |
| 6 | M/54 | pT4a, N3b, M0 | 4 | diffuse | TG | s-SSI | S-1 (12 months) | 1,313 | died, BM |
| 7 | M/72 | pT4a, N2, M0 | 3 | diffuse | DG | none | S-1 (10 months) | 498 | died, PC |
| 8 | M/64 | pT4a, N1, M0 | 3 | intestinal | DG | none | S-1 (13 months) | 980 | died, MI |
| 9 | M/47 | pT4a, N3b, M0 | 4 | intestinal | TG | none | S-1 (15 months) | 544 | died, PC |
| 10 | M/57 | pT4a, N3a, M0 | 3 | intestinal | DG | none | S-1 (26 months) | 1,460 | alive, WR |

The histological type was classified using the Laurens system. S-1: 1 M tegafur + 0.4 M gimestat + 1 M otastat potassium; S-1 was administered twice daily at a dose of 80 mg/m$^2$/day for 14 consecutive days, followed by 7 days of rest. W-PTX: paclitaxel (80 mg/m$^2$) was administrated on days 1, 8 and 15 every 4 weeks (for the duration of chemotherapy).

DG = Distal gastrectomy; TG = total gastrectomy; s-SSI = superficial surgical site infection; WR = without recurrence; DLM = distant lymph node metastasis; BM = brain metastasis; MI = myocardial infarction.

Tumours, 7th edition. Toxicity and operative complications were measured by the common toxicity criteria of the National Cancer Institute, version 3.0. Survival analyses were carried out using the Kaplan-Meier method. The survival period was calculated from the operation date to death or the day of the most recent follow-up. Statistical analysis was conducted using the statistical software GraphPad Prism 5 (GraphPad Software Inc., San Diego, Calif., USA).

## Results

We reviewed 10 patients (1 woman and 9 men, mean age 61 years, range 54–73) in the treatment group. Patient characteristics are summarized in table 1.

*Toxic Effects*

There was no mortality during the postoperative period. The hematological and non-hematological toxic effects of IPC are listed in table 2.

Two patients had G3 anemia, both of whom recovered rapidly without requiring a blood transfusion, and 1 patient who had G3 neutropenia did not need granulocyte colony-stimulating factor support. None of the patients experienced abdominal pain related to IPC.

*Operative Complications*

Grade 2 operative complications related to infection of the superficial surgical site occurred in only 1 patient who was subsequently treated with antibiotics. Other complications, including anastomotic leakage, pancreatic fistula, splenic infarction, pancreatitis, intra-abdominal abscess, postoperative pneumonia, pulmonary embolism, etc., did not develop.

**Table 2.** Toxicity of IPC

| | Grade (CTCAE version 3.0) | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 3/4 |
| Bone marrow | | | | | |
| Leukopenia | 4 | 2 | 0 | 0 | 0 |
| Neutropenia | 2 | 1 | 1 | 0 | 1 |
| Anemia | 3 | 5 | 2 | 0 | 2 |
| Thrombocytopenia | 4 | 1 | 0 | 0 | 0 |
| Laboratory | | | | | |
| AST | 7 | 1 | 0 | 0 | 0 |
| ALT | 4 | 3 | 1 | 0 | 1 |
| Bilirubin | 2 | 1 | 1 | 0 | 1 |
| BUN | 0 | 0 | 0 | 0 | 0 |
| Creatinine | 3 | 0 | 0 | 0 | 0 |
| Fatigue | 0 | 0 | 0 | 0 | 0 |
| Anorexia | 0 | 0 | 0 | 0 | 0 |
| Nausea/vomiting | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 0 | 0 | 0 | 0 | 0 |
| Abdominal pain | 0 | 0 | 0 | 0 | 0 |
| Rash | 0 | 0 | 0 | 0 | 0 |
| Mucositis | 0 | 0 | 0 | 0 | 0 |
| Neuropathy | 0 | 0 | 0 | 0 | 0 |

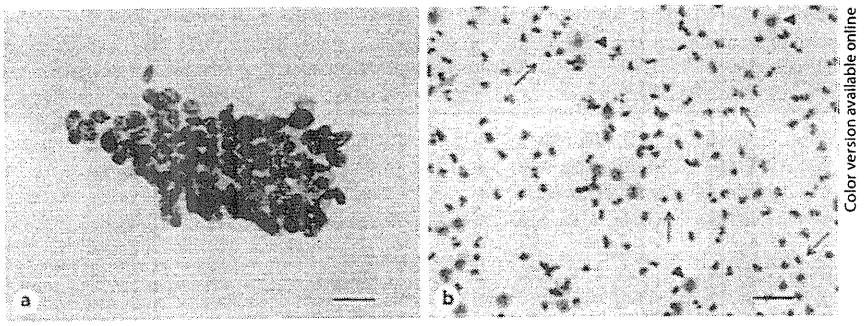


**Fig. 1.** Cytological findings on examination of intraperitoneal free cancer cells. **a** Before IPC, intraperitoneal free cancer cells with hyperchromatic nucleoli and an elongated tubular morphology were observed. **b** Twenty-four hours after IPC administration, the nuclei of the intraperitoneal cancer cells show homogeneous masses and are pyknotic, similar to apoptosis (arrows); no viable cancer cells were detected. Small numbers of mesothelial cells (arrowheads) surround these 'apoptotic' cancer cells. Scale bars: 25.00 μm.

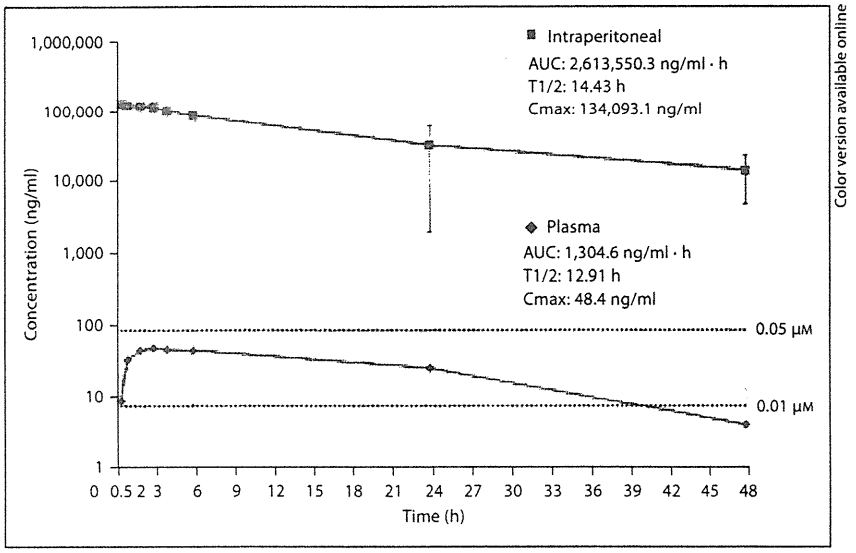


**Fig. 2.** Pharmacokinetic analysis of the intraperitoneal and plasma concentrations of paclitaxel. High intraperitoneal concentrations were maintained for 48 h, during which time the mean plasma peak levels reached the cytotoxic threshold. The intraperitoneal maximum drug concentration (Cmax) was, on average, 2,770.5 times higher than the plasma Cmax. There was no difference in the half-lives (T1/2) determined from the intraperitoneal and plasma concentrations.

*Effectiveness of IPC for Intraperitoneal Free Cancer Cells*

Before IPC, free intraperitoneal cancer cells showed an elongated tubular morphology or were single, exfoliated cells that possessed prominent, hyperchromatic nucleoli. After 24 and 48 h, no viable cancer cells were detected (fig. 1a, b).

*Pharmacokinetic Analysis*

High intraperitoneal drug concentrations were observed over a long period, and mean plasma peak levels did not reach the cytotoxic threshold level of 0.1 μmol/l. The maximal intraperitoneal concentration was, on average, 6,773 times higher than the maximal plasma concentration, which was reached after 0.5 h. The ratio of AUC peri/AUC pla was 2,003.3:1. Figure 2 shows the curves of mean (±SD) intraperitoneal and plasma paclitaxel concentrations versus time in these patients.

*Patient Follow-Up Data*

Patient follow-up data are summarized in table 1. For adjuvant chemotherapy, 9 patients received systemic chemotherapy that included S-1 (1 M tegafur + 0.4 M gimestat + 1 M otastat potassium; administered orally twice daily at a dose of 80 mg/m$^2$/day), while 1 patient (No. 4), who did not give informed consent, did not undergo further treatment until death. No patient was lost to follow-up. After a median follow-up period of 886 days (range 498–

1,742), the median survival time was 1,151 days. The 2-year and 3-year survival rates were 70 and 56.0%, respectively, in the treatment group (fig. 3). In the control group, the median survival time was 392 days. Survival was significantly lower in the latter group than in the treatment group ($p < 0.01$).

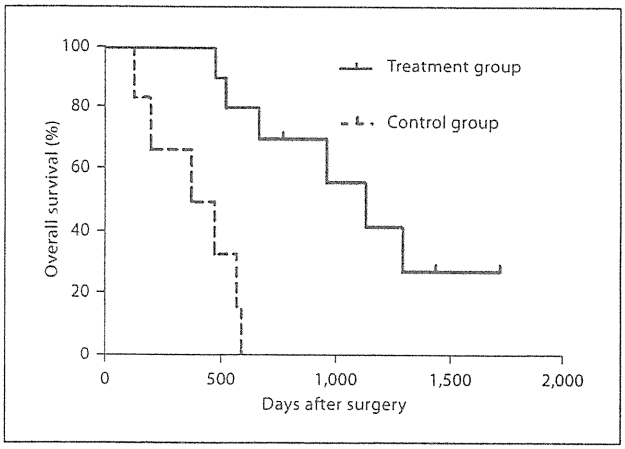


**Fig. 3.** Overall survival of gastric cancer patients who had free cancer cells in the peritoneal cavity and underwent surgery followed by IPC. In the treatment group, the median survival was 1,151 days, with a 2-year survival rate of 70.0%. In the control group, the median survival was 395 days, with a 2-year survival rate of 22.2%.

## Discussion

Several clinical studies have demonstrated the favorable pharmacokinetics of paclitaxel during intraperitoneal instillation chemotherapy [8–11]. The IPC exposure advantage is best expressed as the maximal concentration and the AUC ratios of the drug between the peritoneal cavity and the peripheral blood [18]. For paclitaxel, the average maximal concentration and AUC ratios are between 550:1 and 2,000:1 [8–11]. Therefore, intraperitoneal administration of paclitaxel seems to be effective for free intraperitoneal cancer cells. The penetration depth of paclitaxel was, however, limited [12]. We therefore decided that patients without any other non-curative factors than positive CFPW who underwent gastrectomy had a good indication for use of this modality. Consequently, we administered intraperitoneal paclitaxel immediately after gastrectomy.

However, gastrectomy with systemic lymphadenectomy with D2 dissection requires omentectomy and dissection of the retroperitoneum, and this may promote paclitaxel clearance from the peritoneal cavity. We therefore thought that the maximum concentration and AUC ratios of paclitaxel would be different in patients without surgery. However, in the present study, although limited to 5 cases, the pharmacokinetic data of these cases were similar to those obtained after intraperitoneal paclitaxel instillation without surgery [8], and serum paclitaxel concentrations did not reach concentrations considered to induce hematological toxicity (0.1 μM) [19]. Additionally, the patient who had G3 neutropenia did not need granulocyte colony-stimulating factor support. Our results suggest that IPC with paclitaxel is safe for patients undergoing gastrectomy with D2 lymphadenectomy.

Intraperitoneal drainage is necessary after gastrectomy. However, immediate drainage after IPC led to lower intra-abdominal concentrations of paclitaxel and was considered ineffective for the treatment of free cancer cells. Thus, we clamped all the drainage tubes for 24 h after drug administration. Cytologically, 24 and 48 h after drug administration, no viable cancer cells were detected in the intra-abdominal fluid. In addition, the postoperative complications were mild in patients treated with paclitaxel after gastrectomy with D2 lymphadenectomy. These data suggest that 24-hour clamping of the drainage tube was safe and effective for the eradication of free peritoneal cancer cells.

In our study, the median survival time was 1,151 days, and the 2-year survival rate was 70%. Fukagawa et al. [20] reported that the 2-year survival rate of the patients who underwent gastrectomy without any other non-curative factors than positive CFPW was 25.3% overall. Kodera et al. reported a 2-year survival rate of 47% with the combination of D2 dissection and postoperative S-1 monotherapy in a phase II study that involved 47 patients with a similar clinical status. In addition, in comparison with the control group, the treatment group in our study had a significantly longer survival time. Although our study size was small, these results suggest that our new treatment technique is feasible and may improve the prognosis in post-gastrectomy patients who lack non-curative factors other than positive CFPW.

Limited penetration depth may, however, lead to persistence of occult, viable tumor cells in deeper layers of the peritoneum [12]. This problem may explain the recurrent PC encountered in 3 of our patients. Therefore, patients in whom the only non-curative factor following gastrectomy is positive CFPW might be good candidates for IPC.

We also suggest that gastric cancer patients with grade T3 (invasion of the subserosa) or T4a (invasion of the serosa) tumors, who frequently develop recurrence of PC [21, 22], might benefit from IPC after gastrectomy with D2 lymphadenectomy.

In conclusion, IPC with paclitaxel is an effective treatment modality for free intraperitoneal cancer cells and an interesting approach for gastric cancer patients who underwent gastrectomy without any other non-curative factors apart from positive CFPW. However, further prospective, larger-scale studies are needed to evaluate whether this approach improves survival or even reduces PC recurrence [23].


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## Disclosure Statement

We declare that we have no conflict of interest in connection with this paper.

## References


1 Hundahl SA, Menck HR, Mansour EG, Winchester DP: The National Cancer Data Base report on gastric carcinoma. Cancer 1997; 80:2333–2341.

2 Siewert JR, Bottcher K, Roder JD, Busch R, Hermanek P, Meyer HJ: Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. Br J Surg 1993;80:1015–1018.

3 Allum WH, Powell DJ, McConkey CC, Fielding JW: Gastric cancer: a 25-year review. Br J Surg 1989;76:535–540.

4 Suzuki T, Ochiai T, Hayashi H, Nakajima K, Yasumoto A, Hishikawa E, Shimada H, Horiuchi F, Ohki S, Isono K: Importance of positive peritoneal lavage cytology findings in the stage grouping of gastric cancer. Surg Today 1999;29:111–115.

5 Kodera Y, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K, Morimoto T, Kato T: Peritoneal washing cytology: prognostic value of positive findings in patients with gastric carcinoma undergoing a potentially curative resection. J Surg Oncol 1999;72:60–64, discussion 64–65.

6 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; 83:672–674.

7 Bentrem D, Wilton A, Mazumdar M, Brennan M, Coit D: The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection. Ann Surg Oncol 2005;12:347–353.

8 Markman M, Rowinsky E, Hakes T, Reichman B, Jones W, Lewis JL Jr, Rubin S, Curtin J, Barakat R, Phillips M, et al: Phase I trial of intraperitoneal taxol: a Gynecologic Oncology Group study. J Clin Oncol 1992;10:1485–1491.

9 Hofstra LS, Bos AM, de Vries EG, van der Zee AG, Willemsen AT, Rosing H, Beijnen JH, Mulder NH, Aalders JG, Willemse PH: Kinetic modeling and efficacy of intraperitoneal paclitaxel combined with intravenous cyclophosphamide and carboplatin as first-line treatment in ovarian cancer. Gynecol Oncol 2002;85:517–523.

10 Francis P, Rowinsky E, Schneider J, Hakes T, Hoskins W, Markman M: Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: a Gynecologic Oncology Group pilot study. J Clin Oncol 1995;13: 2961–2967.

11 Mohamed F, Marchettini P, Stuart OA, Yoo D, Sugarbaker PH: A comparison of hetastarch and peritoneal dialysis solution for intraperitoneal chemotherapy delivery. Eur J Surg Oncol 2003;29:261–265.

12 Kyle AH, Huxham LA, Yeoman DM, Minchinton AI: Limited tissue penetration of taxanes: a mechanism for resistance in solid tumors. Clin Cancer Res 2007;13:2804–2810.

13 Yoshikawa T, Omura K, Kobayashi O, Nashimoto A, Takabayashi A, Yamada T, Yamaue H, Fujii M, Yamaguchi T, Nakajima T: A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study). Eur J Surg Oncol 2010;36:546–551.

14 Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, Haag C, Mauer ME, Hasan B, Welch J, Ott K, Hoelscher A, Schneider PM, Bechstein W, Wilke H, Lutz MP, Nordlinger B, Cutsem EV, Siewert JR, Schlag PM: Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010;28:5210–5218.

15 Japanese Gastric Cancer Association: Japanese Classification of Gastric Carcinoma – 2nd English Edition. Gastric Cancer 1998;1: 10–24.

16 Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y: Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 2006;9:14–18.

17 Longnecker SM, Donehower RC, Cates AE, Chen TL, Brundrett RB, Grochow LB, Ettinger DS, Colvin M: High-performance liquid chromatographic assay for taxol in human plasma and urine and pharmacokinetics in a phase I trial. Cancer Treat Rep 1987; 71:53–59.

18 de Bree E, Rosing H, Filis D, Romanos J, Melisssourgaki M, Daskalakis M, Pilatou M, Sanidas E, Taflampas P, Kalbakis K, Beijnen JH, Tsiftsis DD: Cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy with paclitaxel: a clinical and pharmacokinetic study. Ann Surg Oncol 2008;15:1183–1192.

19 Wiernik PH, Schwartz EL, Strauman JJ, Dutcher JP, Lipton RB, Paietta E: Phase I clinical and pharmacokinetic study of taxol. Cancer Res 1987;47:2486–2493.

20 Fukagawa T, Katai H, Saka M, Morita S, Sasajima Y, Taniguchi H, Sano T, Sasako M: Significance of lavage cytology in advanced gastric cancer patients. World J Surg 2010;34: 563–568.

21 Roviello F, Marrelli D, de Manzoni G, Morgagni P, Di Leo A, Saragoni L, De Stefano A: Prospective study of peritoneal recurrence after curative surgery for gastric cancer. Br J Surg 2003;90:1113–1119.

22 Otsuji E, Kuriu Y, Ichikawa D, Okamoto K, Hagiwara A, Yamagishi H: Characteristics of gastric carcinoma invading the muscularis propria. J Surg Oncol 2005;92:104–108.

23 Kodera Y, Imano M, Yoshikawa T, Takahashi N, Tsuburaya A, Miyashita Y, Morita S, Nakao A, Sakamoto J, Sasako M: A randomized phase II trial to test the efficacy of intra-peritoneal paclitaxel for gastric cancer with high risk for the peritoneal metastasis (INPACT trial). Jpn J Clin Oncol 2011;41: 283–286.

# Safety of Intraperitoneal Administration of Paclitaxel After Gastrectomy With En-Bloc D2 Lymph Node Dissection

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**Background:** The aim of this study was to examine the safety, pharmacokinetics, and cytological efficacy against free intraperitoneal cancer cells of intraperitoneal chemotherapy (IPC) with paclitaxel after gastrectomy with en-bloc D2 lymph node dissection (GD2) in cases of gastric cancer with peritoneal carcinomatosis (PC) and/or positive cytological findings in peritoneal washings (CFPW).
**Methods:** Twenty-one patients with gastric cancer with PC and/or positive CFPW who underwent GD2 were treated with early, post-operative, intraperitoneal paclitaxel. Intra-chemotherapeutic toxicity and operative complication were measured using the common toxicity criteria of the National Cancer Institute, version 3.0. Intraperitoneal and plasma paclitaxel concentrations were measured using a high-performance liquid chromatography assay.
**Results:** Grade 3 anemia occurred in two patients (9.5%) and neutropenia was observed in three patients (14.3%). No grade 4 toxicity was observed. A grade 2 operative complication was a superficial surgical site infection (4.8%) that was treated with antibiotics. Cytologically, no viable cancer cells were observed in the intra-abdominal fluid 24 hr after intraperitoneal administration of paclitaxel. The intraperitoneal/plasma area under the drug concentration–time curve (AUC) ratio was 596.9:1.
**Conclusion:** IPC with paclitaxel after GD2 is a safe and cytologically effective treatment modality for free intraperitoneal cancer cells. However, additional data are required to determine the effect on survival.
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KEY WORDS: **peritoneal carcinomatosis; positive cytological findings in peritoneal washings; pharmacokinetics; cytology**

## INTRODUCTION

Gastric cancer is a life-threatening disease worldwide. Recent advances in the treatment of gastric cancer have improved clinical outcomes [1]; however, gastric cancer patients with peritoneal carcinomatosis (PC) still have a poor overall prognosis [2]. Moreover, even in patients with gastrectomy without any other non-curative factors besides positive cytological findings in peritoneal washings (CFPW), estimated 2- and 5-year survival rates were just 25.3 percent and 7.8 percent, respectively [3]. Therefore, a new, definitive treatment modality has been sought to improve survival in these patients.

There is no standard treatment for patients with PC and positive CFPW. Paclitaxel has delayed clearance from the peritoneal cavity because of its high molecular weight and bulky structure. Therefore, some investigators speculated about the possible effectiveness of paclitaxel for intraperitoneal chemotherapy (IPC) [4–7]. The advantage of IPC exposure is best expressed as the maximal concentration and the AUC ratios of the drug between the peritoneal cavity and the peripheral blood [8]. For paclitaxel, the average maximal concentration and AUC ratios are approximately 550:1–2,000:1 [4–7]. The clinical effects of this drug have been verified by a clinical trial in unresectable gastric cancer with PC [9]. However, no clinical report has been produced that describes intraperitoneal administration of paclitaxel after gastrectomy.

Therefore, the aim of this preliminary study was to examine the safety, cytological efficacy for free intraperitoneal cancer cells and pharmacokinetics of IPC after gastrectomy with en-bloc D2 lymph node dissection in patients with gastric cancer and PC and/or positive CFPW.



## MATERIALS AND METHODS

### Patient Selection

We designed a prospective clinicopathological study. We reviewed all patients with gastric cancer and histologically confirmed PC and/or positive CFPW, initially diagnosed at laparotomy, all of whom had gastrectomy with systemic lymphadenectomy and D2 dissection in our department between 2004 and 2009.

Consequently, all patients met the following eligibility criteria that are frequently used in conventional clinical trials [10,11]: (1) histologically proven gastric adenocarcinoma; (2) adequate bone marrow function (leucocyte count 3,000–12,000 $mm^3$, neutrophil

Abbreviations: PC, peritoneal carcinomatosis; CFPW, cytological findings in peritoneal washings; IPC, intraperitoneal chemotherapy; GD2, gastrectomy with en-bloc D2 lymph node dissection.

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count $\geq$1,500/mm$^3$, platelet count $\geq$100,000/mm$^3$); (3) adequate liver function (total serum bilirubin $\leq$1.5 mg/dl and serum transaminase $\leq$2 times the upper limit of normal); (4) adequate renal function (serum creatinine $\leq$1.5 mg/dl); (5) Eastern Clinical Oncology Group Scale performance status 1 or less; (6) aged 20–75 years; (7) no other severe medical conditions or active malignancies; and (8) no previous systemic chemotherapy.

In accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983, written informed consent was obtained from the patients at operation. Patients predicted to be eligible were informed about the therapeutic strategy before surgery, emphasizing its potential benefits as well as the possible risk of mortality and morbidity, prior to operation. Informed consent was given by all patients.

### Cytopathology

Specimens for cytological examination were obtained at laparotomy before manipulation of the tumor. Isotonic saline (100 ml) was instilled into the left sub-diaphragmatic area and pelvis. After manual agitation, the washings were retrieved by aspiration. For cytological examination, the washings were centrifuged for 3 min, and direct smears were prepared and fixed in 95 percent ethanol. Two slides were prepared for each patient and stained using the Papanicolaou method. All slides were reviewed independently by two cytopathologists.

To investigate the efficacy of intraperitoneal administration of paclitaxel, intra-abdominal fluid collected from the drainage tube inserted in the foramen of Winslow and/or in the left sub-diaphragmatic area was examined 6, 24, and 48 hr after intraperitoneal administration of paclitaxel using the same methodology in the 20 patients who gave informed consent. Adequate cytological examination of the sample of intraperitoneal liquid could not be undertaken 48 hr later in just one patient.

### Gastrectomy With En-Bloc D2 Lymph Node Dissection

The surgical procedure was either total gastrectomy for proximal tumors or subtotal gastrectomy when the primary tumor was located distally in the stomach, with a 5 cm "safe" margin. In all cases an en-bloc D2 lymph node dissection was performed according to the Japanese Gastric Cancer Association guidelines [12].

For total gastrectomy, if the tumor did not involve the greater curvature, there was no direct invasion of the pancreas or spleen and there were no apparent nodal metastases in the splenic hilum or along the splenic artery, the spleen was preserved [13].

### Early Post-Operative IPC

For IPC, paclitaxel was administered at a dose of 80 mg/m$^2$ (which corresponds to the weekly intravenous dose of paclitaxel [14]). In each patient, paclitaxel (dissolved in isotonic saline to a final volume of 1 L) was instilled into the peritoneal cavity at the end of the operation through the almost completely closed incision. All drainage tubes within the abdominal cavity were clamped for 48 hr after drug instillation in the first five patients. In the remaining patients, drainage tubes were clamped for 24 hr after drug instillation.

### Pharmacokinetic Analysis

Pharmacokinetic studies were performed on 11 patients who gave informed consent. Peritoneal samples from the drainage tube inserted in the foramen of Winslow and/or in the left sub-diaphragmatic region and plasma samples were obtained during drug administration and 0.5, 1, 2, 3, 4, 6, 24, and 48 hr after drug instillation. Samples were collected in heparinized tubes, centrifuged, and the supernatant stored at −20°C until required. Paclitaxel concentrations were measured using a high-performance liquid chromatography assay as previously described [15]. The AUC from 0 to 48 hr in the peritoneal fluid (AUC peri, 0–48 hr) and in plasma (AUC pla, 0–48 hr) was estimated using the trapezoidal method.

The clinicopathologic classifications were determined according to the criteria of the TNM Classification of Malignant Tumors, 7th edition. Toxicity and operative complication was measured by the common toxicity criteria of the National Cancer Institute, version 3.0. Survival analyses were performed using the Kaplan–Meier method. The survival period was calculated from the operation date to death or the day of most recent follow-up.

## RESULTS

We reviewed 21 cases (7 women and 14 men, mean age = 56.3 years; range: 32–73 years) in this retrospective study. Patient characteristics are summarized in Table I.

### Toxic Effects

There was no mortality during the post-operative period (within 30 days after surgery). The hematological and non-hematological toxic effects of IPC are listed in Table II.

Three patients had G3 neutropenia, but did not need granulocyte colony-stimulating factor support and two patients had G3 anemia, both of whom recovered rapidly without requiring a blood transfusion. None of the patients experienced abdominal pain related to IPC.

### Operative Complications

No patient required a splenectomy. Grade 2 operative complication related to infection of the superficial surgical site occurred in only one patient. This patient was treated with antibiotics. Other complications, for example, anastomotic leakage, pancreatic fistula, intra-abdominal abscess, and post-operative pneumonia, etc. were not seen.

### Effectiveness of IPC for Free Intraperitoneal Cancer Cells

Before IPC, free intraperitoneal cancer cells showed an elongated tubular morphology, or were single, exfoliated cells that possessed prominent, hyper-chromatic nucleoli. Six hours after intraperitoneal administration of paclitaxel, cancer cells showed vacuolization of the cytoplasm and abnormal morphology. After 24 and 48 hr, no viable cancer cells were detected (Fig. 1A,B).

### Pharmacokinetic Analysis

High intraperitoneal drug concentrations were observed over a long period and mean plasma peak levels did not reach the cytotoxic threshold level of 0.1 μmol/L. The maximal intraperitoneal concentration was, on average, 6896.2 times higher than the maximal plasma concentration, which was reached after 0.5 hr. The ratio of AUC peri/AUC pla was 596.9:1. Figure 2 shows the curves of mean (±SD) intraperitoneal and plasma paclitaxel concentrations versus time, in these patients (Fig. 2).

TABLE I. Overall Characteristics of 21 Gastric Cancer Patients

| Patients (number) | Gender/age | Type of resection | TNM stage | CFPW | PC |
|---|---|---|---|---|---|
| #1 | M/40 | TG | pT4a, N3b | Positive | Positive |
| #2 | F/50 | TG | pT3, N1 | Positive | Positive |
| #3 | M/53 | TG | pT4a, N3b | Positive | Positive |
| #4 | F/32 | TG | pT4a, N0 | Positive | Positive |
| #5 | F/49 | TG | pT4a, N3a | Positive | Positive |
| #6 | F/56 | TG | pT4a, N3b | Positive | Positive |
| #7 | M/56 | DG | pT3, N2 | Positive | Negative |
| #8 | F/66 | DG | pT4a, N3a | Positive | Negative |
| #9 | F/59 | TG | pT4a, N1 | Positive | Positive |
| #10 | M/64 | TG | pT3, N3a | Positive | Negative |
| #11 | M/73 | DG | pT3, N3b | Positive | Positive |
| #12 | M/73 | DG | pT4a, N3b | Positive | Negative |
| #13 | M/63 | DG | pT4a, N2 | Positive | Positive |
| #14 | M/55 | TG | pT4a, N3a | Positive | Negative |
| #15 | M/54 | TG | pT4a, N3b | Positive | Negative |
| #16 | M/72 | DG | pT4a, N2 | Positive | Negative |
| #17 | M/64 | DG | pT4a, N1 | Positive | Negative |
| #18 | M55 | TG | pT4a, N2 | Positive | Positive |
| #19 | M/47 | TG | pT4a, N3b | Positive | Negative |
| #20 | M/57 | DG | pT4a, N3a | Positive | Negative |
| #21 | F/44 | TG | pT3, N3b | Positive | Positive |

DG, distal gastrectomy; TG, total gastrectomy; CFPW, cytological findings in peritoneal washings; PC, peritoneal carcinomatosis.
TNM classifications were determined according to the criteria of the TNM classification of malignant tumors, 7th edition.

### Patient Follow-Up Data

As adjuvant chemotherapy, every patient with one exception received systemic combination chemotherapy that included S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium; administered orally twice daily at a dose of 80 mg/m$^2$/day). No patient was lost to follow-up. The median survival time (MST) was 731 days. The 1-year and 3-year survival rates were 90.5% and 29.8%, respectively (Fig. 3).

## DISCUSSION

Gastrectomy with systemic lymphadenectomy and D2 dissection requires omentectomy and dissection of the retro-peritoneum. The omentum is the principal site where ascites is absorbed [16,17]. Therefore, this may promote paclitaxel clearance from the peritoneal cavity. We have thus speculated that the maximal concentration and AUC ratios of paclitaxel would be different in patients with and without surgery.

However, in the present study, the pharmacokinetic data were similar to those obtained after intraperitoneal paclitaxel instillation without surgery [4], and serum paclitaxel concentrations did not reach concentrations considered to induce hematological toxicity (0.1 μM) [18]. Additionally, the patient who had G3 neutropenia did not need granulocyte colony-stimulating factor support. Our results indicate that IPC with paclitaxel is safe for patients undergoing gastrectomy with systemic lymphadenectomy and D2 dissection.

In this study, all patients that had gastric cancer in the proximal part of the stomach showed no tumor on the greater curvature, no direct invasion of the pancreas or spleen and no apparent nodal metastasis in the splenic hilum or along the splenic artery. We therefore performed TG without splenectomy.

Lymph nodes in the splenic hilum are classified as level N2 in proximal gastric cancer, according to the Japanese classification [12]. However, even if curative resection is performed, the patients with metastases in splenic hilar lymph nodes had a very poor prognosis [19]. Additionally, the impact on patient survival is uncertain and splenectomy has a relatively high postoperative morbidity and mortality [20]. Furthermore, gastric cancer patients with PC and/or positive CFPW had a very poor prognosis [2,3]. Therefore, we did not perform preventive splenectomy in these cases.

In our data, the post-operative complications in patients treated with paclitaxel after gastrectomy with systemic lymphadenectomy with D2 dissection were minimal. Only one patient developed infection of the surgical site (Grade 2). There was no mortality during the post-operative period. From the perspective of post-operative complications, IPC with paclitaxel is safe in patients who undergo gastrectomy with systemic lymphadenectomy with D2 dissection, using our approach.

Intraperitoneal drainage is necessary after gastrectomy. However, immediate drainage after IPC led to lower intra-abdominal concentrations of paclitaxel, and was considered ineffective for the treatment of free cancer cells. Thus, initially, we clamped all the

TABLE II. Toxicity of IPC

| | Grade (CTCAE Ver. 3.0) | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 3/4 |
| Bone marrow | | | | | |
| Leucopenia | 5 | 2 | 1 | 0 | 0 |
| Neutropenia | 2 | 1 | 3 | 0 | 3 |
| Anemia | 9 | 9 | 2 | 0 | 2 |
| Thrombocytopenia | 9 | 1 | 0 | 0 | 0 |
| Laboratory | | | | | |
| AST | 16 | 1 | 0 | 0 | 0 |
| ALT | 11 | 5 | 1 | 0 | 1 |
| Bilirubin | 3 | 4 | 1 | 0 | 1 |
| Creatinine | 3 | 0 | 0 | 0 | 0 |
| Fatigue | 0 | 0 | 0 | 0 | 0 |
| Anorexia | 0 | 0 | 0 | 0 | 0 |
| Nausea/vomiting | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 0 | 0 | 0 | 0 | 0 |
| Abdominal pain | 0 | 0 | 0 | 0 | 0 |
| Rash | 0 | 0 | 0 | 0 | 0 |
| Mucositis | 0 | 0 | 0 | 0 | 0 |
| Neuropathy | 0 | 0 | 0 | 0 | 0 |

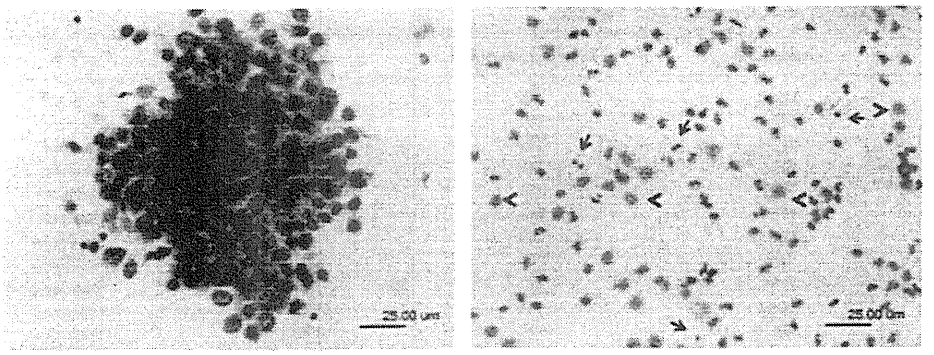

Fig. 1. Cytological findings on examination of intraperitoneal free cancer cells. **A**: Before IPC, intraperitoneal free cancer cells with hyperchromatic nucleoli and an elongated tubular morphology were observed. **B**: Twenty-four hours after IPC administration, the nuclei of the intraperitoneal cancer cells show homogenous masses and were pyknotic, similar to apoptosis (arrow); no viable cancer cells were detected. Small numbers of mesothelial cells (arrow head) surround these "apoptotic" cancer cells.

drainage tubes for 48 hr after drug instillation. However, our data show that no viable cancer cells were detected at 24 and 48 hr after drug instillation. Therefore, in the remaining patients, all the drainage tubes were released at 24 hr after drug instillation. This procedure did not lead to any surgical complications. These data suggest that 24 hr clamping of the drainage tube after drug instillation was effective for the eradication of free cancer cells in the peritoneum.

In this study, we showed a 1-year survival rate of 90.5% with an MST of 24.4 months. The prognosis of patients with PC is extremely poor with a MST of 3–6 months [21,22]. Also the survival time of patients with positive CFWS without macroscopic PC is similar to patients with overt PC [23]. Our data suggest that intraperitoneal administration of paclitaxel after gastrectomy with en-bloc D2 lymph node dissection is an effective treatment for gastric cancer patients with PC and/or positive CFPW.

Penetration of intraperitoneal paclitaxel into the peritoneal surfaces is however limited and the effective diffusion distance into the tissues is reported to be just 100 μm [24]. Therefore patients with very small tumor volumes at the time of IPC may benefit more from IPC. Cases who undergo gastrectomy and do not have non-curative factors apart from positive CFPW might therefore be good candidates for IPC. We also suggest that gastric cancer patients with grade T3 (invasion of the subserosa) or T4a (invasion of the serosa) tumors, who frequently develop recurrence of PC [25,26], might benefit from IPC after gastrectomy with systemic lymphadenectomy and D2 dissection. Additional data are therefore required to determine the large-scale effect of IPC on survival.

## CONCLUSION

IPC with paclitaxel is a safe treatment modality for patients after gastrectomy with systemic lymphadenectomy and D2 dissection, and effective treatment for free intraperitoneal cancer cells. However, prospective studies are needed to evaluate whether this approach improves survival.

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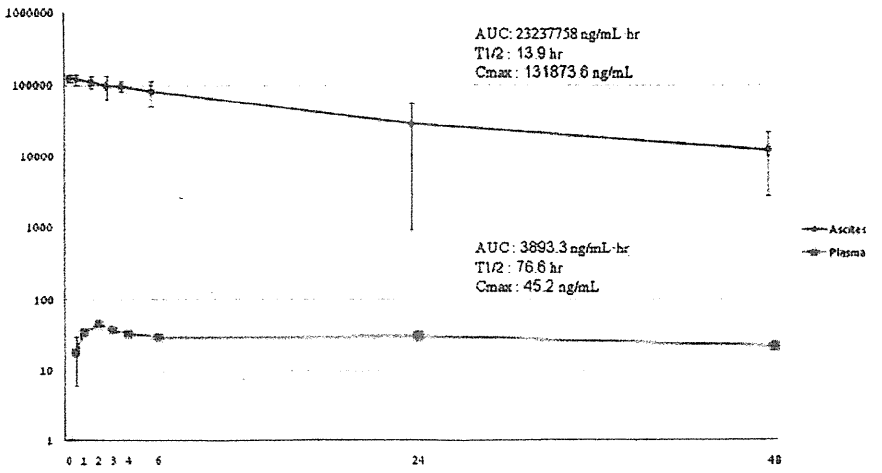


Fig. 2. Pharmacokinetic analysis of the intraperitoneal and plasma concentrations of paclitaxel. High intraperitoneal concentrations were maintained for 48 hr, during which time the mean plasma peak levels reached the cytotoxic threshold. The intraperitoneal maximum drug concentration (Cmax) was, on average, 2917.5 times higher than the plasma Cmax. The plasma half-life (t1/2) was 5.5 times longer than the intraperitoneal half-life (t1/2).

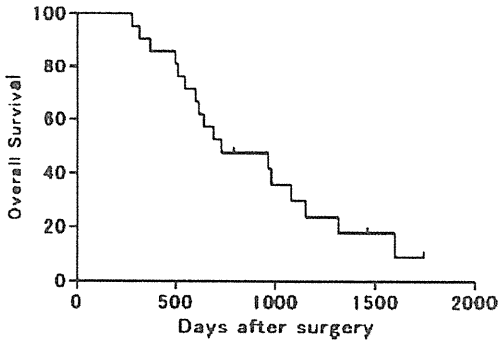


Fig. 3. Overall survival of patients with gastric cancer who had PC and/or positive CFPW and underwent surgery followed by IPC. Median survival was 731 days with a 2-year survival rate of 52.4%.

comments on the manuscript. We also wish to thank Miss. Fusako Kamada for her technical assistance.

## REFERENCES

1. Siewert JR, Bottcher K, Roder JD, et al.: Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. Br J Surg 1993;80: 1015–1018.
2. Allum WH, Powell DJ, McConkey CC, et al.: Gastric cancer: A 25-year review. Br J Surg 1989;76:535–540.
3. Fukagawa T, Katai H, Saka M, et al.: Significance of lavage cytology in advanced gastric cancer patients. World J Surg 2010;34:563–568.
4. Markman M, Rowinsky E, Hakes T, et al.: Phase I trial of intraperitoneal taxol: A Gynecoloic Oncology Group study. J Clin Oncol 1992;10:1485–1491.
5. Hofstra LS, Bos AM, de Vries EG, et al.: Kinetic modeling and efficacy of intraperitoneal paclitaxel combined with intravenous cyclophosphamide and carboplatin as first-line treatment in ovarian cancer. Gynecol Oncol 2002;85:517–523.
6. Francis P, Rowinsky E, Schneider J, et al.: Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: A Gynecologic Oncology Group Pilot Study. J Clin Oncol 1995; 13:2961–2967.
7. Mohamed F, Marchettini P, Stuart OA, et al.: A comparison of hetastarch and peritoneal dialysis solution for intraperitoneal chemotherapy delivery. Eur J Surg Oncol 2003;29:261–265.
8. de Bree E, Rosing H, Filis D, et al.: Cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy with paclitaxel: A clinical and pharmacokinetic study. Ann Surg Oncol 2008;15:1183–1192.
9. Ishigami H, Kitayama J, Kaisaki S, et al.: Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis. Ann Oncol 2010;21:67–70.
10. Yoshikawa T, Omura K, Kobayashi O, et al.: A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study). Eur J Surg Oncol 2010;36:546–551.
11. Schuhmacher C, Gretschel S, Lordick F, et al.: Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010;28:5210–5218.
12. Japanese Gastric Cancer A: Japanese Classification of Gastric Carcinoma—2nd English Edition. Gastric Cancer 1998;1: 10–24.
13. Sano T, Yamamoto S, Sasako M: Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma: Japan Clinical Oncology Group Study JCOG 0110-MF. Jpn J Clin Oncol 2002;32:363–364.
14. Hironaka S, Zenda S, Boku N, et al.: Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 2006;9:14–18.
15. Longnecker SM, Donehower RC, Cates AE, et al.: High-performance liquid chromatographic assay for taxol in human plasma and urine and pharmacokinetics in a phase I trial. Cancer Treat Rep 1987;71:53–59.
16. Lukas G, Brindle SD, Greengard P: The route of absorption of intraperitoneally administered compounds. J Pharmacol Exp Ther 1971;178:562–564.
17. Hirabayashi K, Graham J: Genesis of ascites in ovarian cancer. Am J Obstet Gynecol 1970;106:492–497.
18. Wiernik PH, Schwartz EL, Strauman JJ, et al.: Phase I clinical and pharmacokinetic study of taxol. Cancer Res 1987;47:2486–2493.
19. Shin SH, Jung H, Choi SH, et al.: Clinical significance of splenic hilar lymph node metastasis in proximal gastric cancer. Ann Surg Oncol 2009;16:1304–1309.
20. Yu W, Choi GS, Chung HY: Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer. Br J Surg 2006;93:559–563.
21. Ikeguchi M, Matsumoto S, Yoshioka S, et al.: Laparoscopic-assisted intraperitoneal chemotherapy for patients with scirrhous gastric cancer. Chemotherapy 2005;51:15–20.
22. Kitamura Y, Hayashi K, Sasagawa T, et al.: Pilot study of S-1 in patients with disseminated gastric cancer. Drugs Exp Clin Res 2003;29:125–130.
23. Okabe H, Ueda S, Obama K, et al.: Induction chemotherapy with S-1 plus cisplatin followed by surgery for treatment of gastric cancer with peritoneal dissemination. Ann Surg Oncol 2009;16:3227–3236.
24. Kyle AH, Huxham LA, Yeoman DM, et al.: Limited tissue penetration of taxanes: A mechanism for resistance in solid tumors. Clin Cancer Res 2007;13:2804–2810.
25. Roviello F, Marrelli D, de Manzoni G, et al.: Prospective study of peritoneal recurrence after curative surgery for gastric cancer. Br J Surg 2003;90:1113–1119.
26. Otsuji E, Kuriu Y, Ichikawa D, et al.: Characteristics of gastric carcinoma invading the muscularis propria. J Surg Oncol 2005; 92:104–108.

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分担研究報告書

# 狭窄を伴う根治切除不能胃癌に対する姑息的胃切除術・バイパス術のTS-1ベースの化学療法に対する意義に関する研究

研究分担者　栗田　啓
独立行政法人国立病院機構四国がんセンター副院長

研究要旨　狭窄を伴う切除不能胃癌に対する緩和手術は，術後にTS-1を用いた化学療法を行うことが期待できる有用な治療戦略の１つであると考えられた。

## A．研究目的

進行・再発胃癌に対する初回化学療法では，TS-1+シスプラチン（CDDP）療法が推奨されている．一方，狭窄により経口摂取不能となった切除不能胃癌症例では，QOL の改善や経口抗癌剤の使用が可能となることを期待し，姑息的胃切除術（胃切）やバイパス術（BP）の緩和手術が施行されることも多い．狭窄を伴う根治切除不能胃癌に対する緩和手術の，その後の TS-1 ベース化学療法に対する意義について検討をおこなった．

## B．研究方法

対象は2006年1月～2010年12月に，当科で初回治療として胃切またはBPを施行した狭窄を伴う根治切除不能胃癌52例（胃切13例，BP39例）のうち，術後に化学療法を希望した44例（胃切11例，BP33例）．これらにおいて，後ろ向き解析により，手術合併症，化学療法開始までの日数，TS-1ベース化学療法の治療成功期間（TTF），全生存期間などを検討した．全ての患者には説明と同意を行った後に手術および化学療法などの治療を行い，倫理的配慮を行った．

## C．研究結果

52例における術後合併症は，胃切で心不全，肺炎を各1例に，BPでは胃癌の悪化に伴う肝機能異常，イレウスを各1例に認めた．術後に化学療法を希望した44例のうち，実際に化学療法を施行できた症例は43例（98%）で，術後，化学療法開始までの中央値は35日であった．また，TS-1投与が可能と考えられた症例は39例（89%）であった．実際に施行された化学療法レジメンはTS-1単剤：9例，TS-1+CDDP：21例，その他：13例で，TS-1ベース化学療法施行例は全体で32例であった。TS-1ベース化学療法施行例32例の治療成績について検討すると，TS-1+CDDP療法とTS-1単剤投与例の有害事象では，Grade 3/4の血液毒性を20～30%に認めたが，Grade 3/4の非血液毒性の発現はなく，比較的安全に投与可能であった．32例のTTF中央値は195日であり，有害事象による中

止は肺炎の1例のみで，経過中胃切除術を施行した1例を除き，30例全例が増悪（PD）まで治療継続が可能であった．また，手術からの全生存期間（MST）は406日だった。

D．考察

切除不能胃癌に対する緩和手術は比較的安全に施行でき，約90%の症例でTS-1の投与が可能となった．TS-1ベース化学療法施行例での治療成績は，通常の進行・再発胃癌に対する化学療法の成績と遜色なく良好と考えられた。

E．結論

狭窄を伴う切除不能胃癌に対する緩和手術は，術後にTS-1を用いた化学療法を行うことが期待できる有用な治療戦略の1つであると考えられた。

G．研究発表

2012年2月8日-10日に開かれた第84回日本胃癌学会総会にて発表した。

# Intraperitoneal Docetaxel[Q1] Combined with S-1 for Advanced Gastric Cancer With Peritoneal Dissemination

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**Background:** Our previous phase I study indicated that combination chemotherapy with intraperitoneal docetaxel and S-1 was well tolerated by gastric cancer patients with peritoneal carcinomatosis (PC). This study evaluated the benefits of this combination chemotherapy and subsequent surgery.

**Patients and Methods:** Neoadjuvant Intra-Peritoneal and Systemic chemotherapy (NIPS) was introduced to gastric cancer patients with positive cytology or with PC. Two cycles of intraperitoneal chemotherapy with docetaxel combined with S-1, were administrated and gastrectomy with lymph node dissection was performed in cases without macroscopic PC at post-NIPS staging laparoscopy.

**Results:** Eighteen patients were enrolled in this study. Eight patients had measurable lymph node metastases by the RECIST criteria and computed tomography (CT) showed that five (62.5%) displayed a major response to the treatment. Out of 18 patients, 14 (78%) showed negative results on peritoneal cytology and no macroscopic PC, while the remaining four were cancer cell positive on peritoneal cytology or showed macroscopic PC even after NIPS. The median survival time of the entire group was 24.6 months. No treatment-related mortality was observed during NIPS and surgery.

**Conclusion:** This study indicated that the NIPS combined with surgery was highly active and well tolerated by advanced gastric cancer patients with PC.

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KEY WORDS: **gastric cancer; neoadjuvant chemotherapy; intra-peritoneal chemotherapy; peritoneal lavage cytology; S-1; docetaxel**

## INTRODUCTION

The incidence of gastric cancer has decreased worldwide and particularly so in Western countries. Despite this, it remains the fourth-most common cancer and the second-most common cause of cancer-related deaths [1,2]. Multidisciplinary approaches to the treatment of advanced gastric cancer including chemotherapy, radiotherapy, and surgery have recently been developed and the survival benefits of such treatments are being investigated worldwide [3,4]. Furthermore, several novel chemotherapeutic agents including taxans (paclitaxel and docetaxel), irinotecan, oxaliplatin, S-1, and capecitabine have shown activity in gastric cancer [5–10].

Peritoneal carcinomatosis (PC) is the most frequent mode of recurrence and is responsible for about 60% of all deaths from gastric cancer [11]. Gastric cancer patients with PC are considered to be non-curable and are usually treated with systemic chemotherapy without surgical resection. Few clinical trials have been performed thus far for gastric cancer with PC. The Japanese Clinical Oncology Group conducted a multicenter phase III study of sequential chemotherapy with methotrexate and 5-FU (MF) compared with 5-FU continuous infusion therapy (5-FU) that included 237 gastric cancer patients with PC [12]. The median survival time (MST) was 10.6 months for MF and 9.4 months for 5-FU. Recent randomized clinical trials have proposed several standards for combination chemotherapy for non-curable gastric cancer such as docetaxel, cisplatin, and fluorouracil (DCF) in the United States, epirubicin, cisplatin, and fluorouracil (ECF) in Europe, or fluoropyrimidine (S-1) and cisplatin in Japan [13–15]. However, the MSTs in these studies were 8.9, 9.2, and 13 months, respectively, and a new-multidisciplinary approach for gastric cancer with PC is therefore needed.

S-1 is an oral fluorpyrimidine derivative consisting of tegafur, gimestat (CDHP), which has dihydropyrimidine dehydrogenase (DPD)-inhibiting activity, and otastat potassium (Oxo), which reduces its gastrointestinal toxicity. In Japan, adjuvant chemotherapy with S-1 has been a standard therapy after curative surgery for Stage II and III gastric cancer due to the multicenter phase III randomized trial [16]. We reported previously that oral intake of S-1 was highly effective against gastric PC due to the higher concentrations of 5-FU and CDHP achieved in peritoneal tumors than in plasma in a mouse model [17]. The efficacy of S-1 for gastric cancer patients with PC has also been reported [18]. Furthermore, the safety and a significant pharmacological advantage with intraperitoneal docetaxel have been proven [19]. The combination of S-1 and intravenous docetaxel has been reported as a promising therapy for advanced gastric cancer reported by Yoshida and Yamaguchi [20,21].

We recently reported the feasibility of S-1 and intraperitoneal docetaxel combination chemotherapy for patients with positive cytology on peritoneal lavage specimens or with macroscopically visible peritoneal metastasis [22]. The regimen was found to be very safe and promising for gastric cancer patients with peritoneal dissemination. The purpose of this prospective study was to investigate the efficacy of this newly developed combination chemotherapy with

Conflict of interest: None.

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subsequent surgery for gastric cancer with positive peritoneal lavage cytology and/or macroscopic peritoneal dissemination.

## MATERIALS AND METHODS

### Patient Selection

The eligibility for this study was as follows: (i) Histopathological confirmation of gastric cancer; (ii) a positive result on peritoneal cytology or macroscopic PC diagnosed by staging laparoscopy; (iii) the absence of non-curative factors such as distant metastasis to liver or lung except of peritoneum; (iv) performance status [Eastern Cooperative Oncology Group (ECOG)] of less than two; (v) age of less than 75; (vi) no prior treatment; (vii) adequate bone marrow function (leukocyte count more than 3,000 $ml^{-1}$ and platelet count more than 100,000 $ml^{-1}$); (viii) adequate liver function (serum bilirubin level less than 1.5 mg $dl^{-1}$ and serum transaminase levels less than two times the upper limit of normal); (ix) adequate renal function (serum creatinine level less than 1.5 mg $dl^{-1}$; (x) no other severe medical conditions such as symptomatic infectious disease, intestinal pneumonia, active hemorrhage/bleeding, or obstructive bowel disease; (xi) not pregnant or lactating; and, (xii) provision of written informed consent in accordance with government guidelines of each institution or hospital. This study was approved by the ethics committees of Osaka University Hospital.

### Treatment Strategy

Figure 1 shows the treatment strategies followed in this study. Staging laparoscopy or peritoneal lavage cytology under local anesthesia [23] was performed for gastric cancer patients with serosa-invading tumors diagnosed using multidetector-row computed tomography (CT) and 3-dimensional imaging. Two cycles of neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) was provided to patients with positive cytology and/or peritoneal deposits of cancer metastasis. The staging laparoscopy was mandatory for all patients after chemotherapy and gastrectomy with lymph node dissection was performed in patients without macroscopic peritoneal deposits of cancer metastasis.

### Treatment Protocol

The abdominal cavity was irrigated with various doses of docetaxel dissolved in 1 L of saline on day 1 every three weeks; the saline was administered through a drainage tube placed for the collection of peritoneal lavage diagnosis or staging laparoscopy [22]. The dosage of docetaxel varied from 40 to 50 to 60 $mg/m^2$ due to the progressive inclusion of patients from the phase I study. The S-1 was administered orally at a fixed dose of 40 $mg/m^2$ twice daily on days 1–14 every three weeks. Patients were treated for two cycles before staging laparoscopy and subsequent gastrectomy unless unacceptable toxicity or patient unwillingness was observed.

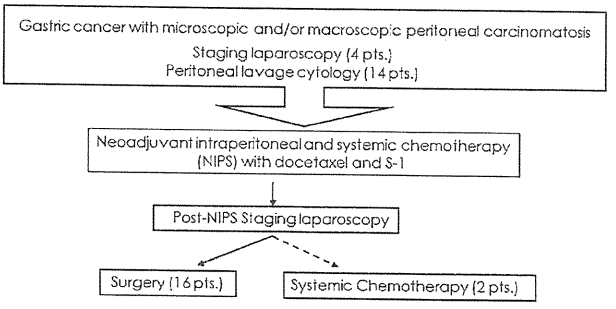


Fig. 1. Flow diagram of the treatment protocol.

### Evaluation of the Disease

Before and after NIPS, conventional examinations including the multidetector-row CT were performed to assess the clinical response. The post-NIPS staging laparoscopy was mandatory to evaluate the effect of the treatment on peritoneal metastasis. Tumor response of measurable metastatic lesions was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [24]. A complete response (CR) was defined as the disappearance of all evidence of cancer for more than four weeks. A partial response (PR) was defined as more than 50% reduction in the sum of the products of the perpendicular diameters of all lesions without any evidence of new regions or progression in any lesions. Stable disease (SD) was defined as less than a 50% reduction or less than a 25% increase in the sum of the products of the perpendicular diameters of all lesions, without any evidence of new lesions. Progressive disease (PD) was defined as more than 25% increase in more than one region or the appearance of new regions. The response in the peritoneum was evaluated by staging laparoscopy or surgery after NIPS. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 3.0 and recorded. Recurrence after surgery including such as peritoneum, liver and distant lymph nodes was diagnosed with CT, which was repeated every 3 months.

### Statistical Analysis

Survival was calculated from the initial date of treatment to the occurrence of the event or to the date of the most recent follow-up visit by the Kaplan–Meier method. Univariate analysis was performed using the log-rank test, and multivariate analysis was conducted using the Cox proportional hazards model. A value of $P < 0.05$ was considered statistically significant.

## RESULTS

### Clinicopathological Characteristics of Patients

A total of 18 gastric cancer patients with PC were enrolled in this study representing all patients diagnosed and treated at the Department of Gastroenterological Surgery, Osaka University Hospital between July 2006 and June 2010. All 18 patients showed positive peritoneal cytology with staging laparoscopy (four cases) and peritoneal lavage cytology under local anesthesia (14 cases). Four patients performed with staging laparoscopy were also confirmed to have macroscopic PC. Table I details the clinicopathological characteristics of these patients. The patient group comprised 12 men and six women with a mean age of 62.9 years (range 51–75 years). Macroscopically, type 4 tumors accounted for 78% of the cases (14/18). Histopathologically, undifferentiated tumors including poorly differentiated and signet ring cell carcinoma were dominant (15/18, 83%). Gastrectomy with lymph node dissection was performed in 16 of the 18 patients (89%); these patients showed no macroscopic peritoneal metastasis at the post-NIPS staging laparoscopy. Surgery was not conducted on the remaining two patients because of macroscopic PC in the abdominal cavity. Of the 16 patients who underwent gastrectomy, 13 (81%) underwent total gastrectomy and one of these underwent additional splenectomy because of macroscopic lymph node metastasis in splenic hilum. Therefore, only four of 16 cases (25%) underwent D2 lymphadenectomy, while the remaining 12 had D2 lymphadenectomy without clearance of lymph nodes in splenic hilum classified as D1+ (Table I). All 16 patients who had gastrectomy after NIPS were treated with S-1. Out of two patients who had

**TABLE I. Clinicopathological Characteristics of the 18 Patients Enrolled in the Present Study**

| | |
|---|---|
| Average age, years (range) | 62.9 (51–75) |
| Sex (Male/Female) | 12/6 |
| Tumor type | |
| 3 | 4 |
| 4 | 14 |
| Histology | |
| Diffuse type | 15 |
| Differentiated type | 3 |
| Ascites (CT) | |
| Present | 6 |
| Absent | 12 |
| Type of surgery (16 cases) | 16/18 (88.9%) |
| Total gastrectomy | 13 |
| With splenectomy | 1 |
| Without splenectomy | 12 |
| Distal gastrectomy | 3 |
| Lymph node dissection | |
| D2 | 4 |
| D1+ | 12 |

Type 3: Ulcerated carcinomas without definite limits, infiltrating into the surrounding wall; type 4: Diffusely infiltrating carcinomas in which ulceration is usually not a marked feature [33]. D2: D2 lymphadenectomy, D1+: D2 lymphadenectomy without clearance of lymph nodes in splenic hilum.

no surgery, one suffered from lethal pulmonary thrombosis and another continued systemic chemotherapy with S-1 and docetaxel after NIPS.

## Clinical Response and Toxicity to NIPS

After the NIPS, all patients were evaluated for clinical response and toxicities. Of the 18 patients, 15 (83%) completed two cycles of the combination chemotherapy, whereas the remaining three patients were given only one cycle of the combination chemotherapy because of patient unwillingness in one case, grade 3 fever in one case, and obstruction of the catheter after one cycle in the remaining case. Eight patients showed measurable lymph node metastases according to the RECIST criteria. As shown in Table II, the CT results showed that five out of eight patients (62.5%) displayed a major response (0 CR, 5 PR) to the treatment. Out of the 18 patients, 14 (78%) showed negative results on peritoneal cytology and no macroscopic peritoneal metastasis, while the remaining four patients were still positive on peritoneal cytology after NIPS or showed macroscopic peritoneal metastasis (Table II).

**TABLE II. Anti-Tumor Efficacy of Neoadjuvant Intra-Peritoneal and Systemic Chemotherapy (NIPS)**

| RECIST criteria | n | % |
|---|---|---|
| Measurable disease | 8 | |
| Overall response rate (CR + PR) | 5 | 62.5 |
| CR | 0 | 0 |
| PR | 5 | 62.5 |
| SD | 3 | 37.5 |
| PD | 0 | 0 |
| Non-measurable disease | 10 | |
| Efficacy for peritoneal disease | 18 | |
| CY0 and P0 after NIPS | 14 | 78 |
| CY1 or P1 after NIPS | 4 | 22 |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CY0, peritoneal lavage cytology negative; CY1, peritoneal lavage cytology positive.

Adverse events were graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.0 (Table III). No patients showed grade 4 or higher toxicities, while one patient showed grade 3 leukopenia and neutropenia, and one showed grade 3 fever. No chemotherapy-related mortality was reported.

## Postoperative Complications

Among the 16 patients who underwent surgery, postoperative complications occurred in three patients (19%, Table IV). Postoperative hemorrhage occurred in one patient, who required re-operation, and intra-abdominal abscess occurred in two cases. No surgery-related mortality (30 days mortality) was reported.

## Survival

Figure 2 shows the overall survival time after the introduction of NIPS for all patients enrolled in this study. The MST was 24.6 months, with 76% of patients surviving for 1 year and 54% surviving for 2 years at a median follow-up time of 45 months. Fourteen patients had died by April 21, 2011. Of these, three patients died from non-cancer-related diseases, pulmonary embolism, liver dysfunction, and pneumonia. The remaining 11 patients died from peritoneal recurrence of gastric cancer.

# DISCUSSION

In the present study, we conducted a prospective phase II study to evaluate the efficacy of the same NIPS regime and subsequent surgery in gastric cancer patients with microscopic or macroscopic PC. Following the NIPS treatment, 78% of enrolled patients showed negative results on peritoneal cytology and no macroscopic peritoneal metastasis. The MST of all patients was 24.6 months long. This regimen is also safe and less toxic, which might reflect the pharmacokinetics of intraperitoneally administered docetaxel, i.e., low concentration in the systemic circulation compared to a higher concentration in the abdominal cavity [22,25]. Postoperative complications were observed in three (18.8%) of 16 patients who underwent gastrectomy, which is infrequent compared to the previous reports of surgery after neo-adjuvant chemotherapy [26,27], and no surgery-related mortality was observed. Previously, we reported

**TABLE III. Toxicity Profile[Q2] of Neoadjuvant Chemotherapy in 18 Patients (National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.0: NCI-CTCAE ver. 4.0)**

| Adverse events | n = 18 | | | | |
|---|---|---|---|---|---|
| Grade | 1 | 2 | 3 | Total (%) | Gr. 3% |
| Non-hematological toxicity | | | | | |
| Fatigue | 4 | 4 | 0 | 8 (44) | 0 |
| Anorexia | 4 | 5 | 0 | 9 (50) | 0 |
| Diarrhea | 0 | 1 | 0 | 1 (6) | 0 |
| Rash | 3 | 0 | 0 | 3 (17) | 0 |
| Alopecia | 2 | 0 | 0 | 2 (11) | 0 |
| Fever | 0 | 0 | 1 | 1 (6) | 6 |
| Hematological toxicity | | | | | |
| Leukopenia | 1 | 0 | 1 | 2 (11) | 6 |
| Neutropenia | 1 | 1 | 1 | 3 (17) | 6 |
| Anemia | 2 | 1 | 0 | 3 (17) | 0 |
| Rise in AST | 1 | 0 | 0 | 1 (6) | 0 |
| Rise in ALT | 2 | 0 | 0 | 2 (11) | 0 |
| Elevated serum creatinine | 1 | 0 | 0 | 1 (6) | 0 |

Grade (Gr.) indicates toxicity grade according to the NCI-CTCAE ver. 4.0.