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ORIGINAL ARTICLE

# Conversion Surgery for Gastric Cancer with Peritoneal Metastasis Based on the Diagnosis of Second-Look Staging Laparoscopy

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## Abstract

**Background** Patients with positive peritoneal cytology (CY1) or peritoneal dissemination (P1) have significantly poor prognosis. We performed pre-therapeutic staging laparoscopy (SL) to diagnose peritoneal metastasis for patients with advanced gastric cancer. When peritoneal metastasis disappears by chemotherapy for patients with CY1 or P1, we have intention to perform conversion surgery (CS). This study aims to clarify the clinical significance of CS for such patients.

**Methods** We retrospectively analyzed clinical outcomes of 115 patients with advanced gastric cancer (large type 3, type 4, serosa-invasion) who underwent SL between 2005 and 2014. Disappearance of peritoneal metastasis was confirmed by second-look SL.

**Results** CY0P0, CY1P0, and P1 were found in 56, 26, and 33 patients, respectively. In patients with CY1P0, 12 patients (66.7%) underwent CS (R0) as peritoneal cytology turned negative. All cases received S-1-based regimens, with median five treatment courses. The survival of patients with CS was significantly longer than those without CS (median survival time (MST); 41 vs. 11 months, respectively, $P < 0.001$). We observed no difference in overall survival between patients who underwent CS and patients with CY0P0 at the first SL ($P = 0.913$). All patients with P1 received chemotherapy. As peritoneal metastasis of five patients (15.2%) disappeared by chemotherapy, those patients underwent the CS (R0). The survival of patients who underwent CS was significantly longer than those who did not (MST; 31 vs. 10 months, respectively, $P = 0.034$).

**Conclusion** This study suggests that conversion surgery contributes to improvement in survival of patients with peritoneal metastasis.

**Keywords** Gastric cancer · Conversion surgery · Peritoneal metastasis · Peritoneal cytology · Staging laparoscopy

## Introduction

Gastric cancer is the fifth most common cancer and the third most common cause of cancer-related death worldwide.[1] Prognosis of advanced gastric cancer has recently improved with the introduction of new chemotherapy and molecular targeting therapy, but remains unsatisfactory. In particular, patients with peritoneal metastasis have the poorest prognosis, and peritoneal metastasis is a life-threatening disease with an extremely short survival period in patients with advanced gastric cancer. Positive peritoneal cytology (CY1) of peritoneal lavage fluid is considered to be a poor prognostic factor in gastric cancer;[2,3] it is the same as distant metastasis (M1), regardless of the presence of macroscopic peritoneal dissemination (P1), both in the TNM classification and in the Japanese classification by the Japanese Gastric Cancer Association.[4,5] Moreover, P1 factor is a stronger indicator of prognosis than CY1 factor. Systemic chemotherapy is the standard treatment for unresectable, metastatic gastric cancer or recurrent gastric cancer including peritoneal metastasis.[6,7] It has gradually progressed, and 5 FU- or cisplatin-based regimens are generally accepted as the standard regimens worldwide.[8,9] According to Japanese gastric cancer treatment guidelines, the combination of S-1 (tegafur, gimeracil, oteracil) or capecitabine with cisplatin or oxaliplatin is recommended for first-line chemotherapy.[6,10–12] Although the prognosis of patients receiving systemic chemotherapy has

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steadily improved, median survival time (MST) remains at between only 10 and 16 months.[7,10–13] It is therefore necessary to further advance the survival rate of patients with peritoneal metastasis. On the other hand, conversion from unresectable to resectable metastatic colorectal cancer by advances in systemic chemotherapy, termed "conversion therapy," can reportedly improve the survival.[14–16] Conversion therapy is defined as surgical treatment aimed at curative resection (R0) through post-chemotherapy for tumors originally considered marginally resectable or unresectable for technical or oncological reasons.[17] The term "conversion surgery (CS)" can be applied to surgical treatment performed for conversion therapy, and has potential benefits in terms of patient survival.[18] The feasibility and efficacy of CS, however, is still unclear in patients with unresectable or metastatic gastric cancer, especially those with peritoneal metastasis. Furthermore, the indications for CS, appropriate regimens of chemotherapy, and timing of the operation for CS have not been clarified.

Some reports have showed that patients with large type 3 (tumor diameter ≥ 8 cm), type 4 or serosa-invasion gastric cancer have higher incidence of peritoneal metastasis (19.1–22.2%), and worse survival than those with other types.[19,20] Such patients are therefore considered eligible candidates for pre-therapeutic staging laparoscopy (SL). We performed SL to diagnose peritoneal metastasis for patients with large type 3, type 4, or serosa-invasive gastric cancer. When CY1 or P1 is detected, we perform systemic S-1 based chemotherapy. Based on response to chemotherapy, we perform second-look staging laparoscopy (second-look SL), and when peritoneal metastasis disappears by chemotherapy, we perform CS.

In this study, we retrospectively analyzed the clinicopathologic and survival data clinical outcomes of patients with CY1 or P1, and investigated the clinical significance of CS based on the diagnosis of second-look staging laparoscopy for those patients.

## Material and Methods

### Patients

We retrospectively reviewed a database of patients with advanced gastric cancer (large type 3, type 4, serosa-invasion) who underwent SL at Wakayama Medical University between 2005 and 2014. We examined clinical outcomes of patients with CY1P0 or P1, and the feasibility and efficacy of CS for those patients.

### Patient Evaluation

Diagnosis in all patients histologically confirmed adenocarcinoma of the stomach. Neck, abdominal, and pelvic multi detector-row computed tomography (MDCT) and upper gastrointestinal tract endoscopy were performed to determine the pretreatment clinical stage for all patients. In all cases, peritoneal metastasis and peritoneal cytology were confirmed by staging laparoscopy (SL) under general anesthesia. Peritoneal lavage was performed using each 100 mL of saline into the Douglas pouch and the left subphrenic cavity during SL, and lavage fluids were collected for peritoneal cytology.[21–24] The diagnosis of peritoneal cytology was pathologically examined using Papanicolaou staining. No patients had definite distant metastasis except for peritoneal dissemination and positive peritoneal cytology. Eastern Cooperative Oncology Group performance status was 0–2 in all patients. Tumor staging and histopathologic grading were determined according to the *International Union Against Cancer pathologic tumor, node, metastasis classification system staging guidelines, 7th edition*.[4] We used terminology defined by the Japanese Gastric Cancer Association.[5]

### Chemotherapeutic Schedule

Chemotherapeutic schedules were as follows: The S-1 plus cisplatin (CDDP) regimen (S-1/CDDP) was oral S-1 (40 mg/m$^2$ twice daily) on days 1–21 plus intravenous cisplatin (60 mg/m$^2$) on day 8 of a five-week cycle.[10] The docetaxel, cisplatin, and S-1 (Docetaxel/CDDP/S-1) regimen was intravenous docetaxel (40 mg/m$^2$) and cisplatin (60 mg/m$^2$) on day 1, and oral S-1 (40 mg/ m$^2$, twice daily) for 2 weeks on days 1–14, followed by a two-week rest.[25] The S-1 plus docetaxel regimen (S-1/docetaxel) was intravenous docetaxel (40 mg/m$^2$) on day 1 and oral S-1 (40 mg/m$^2$ twice daily) on days 1–14 of a 21-day cycle.[26]

Chemotherapeutic treatment was discontinued when patients had disease progression, development of severe toxic effects, or rejection of chemotherapy. Clinical tumor responses to chemotherapy were objectively assessed after two treatment courses according to *Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1*.[27] Adverse events were evaluated according to the *Common Terminology Criteria for Adverse Events (CTCAE), version 4.0*.[28]

### Follow-up Schedule

Tumor responses were assessed by MDCT and endoscopy after two treatment courses or earlier in patients with evidence of treatment failure. The tumor markers, such as carcinoembryonic antigen and CA 19-9, were measured every 4–5 weeks during chemotherapeutic treatment. Laboratory tests and physical examinations were performed at least every 2 weeks during treatment.

**Table 1** Clinicopathological features

| | CY0P0 ($n = 56$) | CY1P0 ($n = 26$) | P1 ($n = 33$) | $p$ |
|---|---|---|---|---|
| Gender (male/female) | 40/16 | 16/10 | 21/12 | 0.594 |
| Age | 60 (19–78) | 67 (43–75) | 66 (35–78) | 0.381 |
| Tumor location (U/M/L/whole) | 18/18/7/13 | 4/6/3/13 | 7/8/2/16 | 0.188 |
| Macroscopic type (Well- /Ill-defined) | 2/53 | 1/25 | 0/33 | 0.906 |
| Clinical T (3/4a/4b) | 5/50/1 | 1/24/1 | 2/31/0 | 0.746 |
| Clinical N (0/1, 2, 3) | 8/48 | 4/22 | 8/25 | 0.424 |
| Clinical M (0/1) | 56/0 | 26/0 | 25/8 | < 0.001 |
| Clinical stage (II/III/IV) | 10/46/0 | 4/22/0 | 9/16/8 | < 0.001 |
| Histological type (well-differentiated/undifferentiated) | 21/35 | 6/20 | 4/29 | 0.070 |

## Indications for Conversion Surgery

Indication for CS was prediction of the curative resection on the basis of the clinical responses to chemotherapy. In other words, when the responses to chemotherapy were complete response (CR), partial response (PR), or stable disease (SD), we performed second-look SL. The peritoneal cavity was carefully observed, and peritoneal cytology was then performed for all these patients. When negative conversion in CY1 or P1 was confirmed by second-look SL, we performed CS. The operation was performed within 4 weeks after the last S-1 administration in the last course of chemotherapy. Adjuvant chemotherapy with S-1 agent was administered after CS. Postoperative complications were analyzed using the Clavien–Dindo classification system.[29]

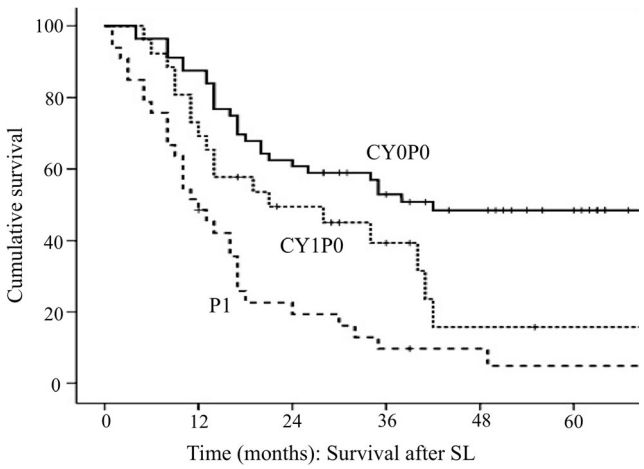


**Fig. 1** Overall survival curves of 115 patients with advanced gastric cancer (type 4, large type 3, serosa-invasion) who underwent staging laparoscopy (SL) among the CY0P0 group (——), the CY1P0 group (– – – –) and the P1group (— — —). Median survival times (MSTs) were 42 months in the CY0P0 group, 21 months in the CY1P0 group, and 12 months in the P1 group. (Median follow-up 20 (1–82) months) (CY0P0 vs CY1P0 *P = 0.038*, CY0P0 vs P1 *P < 0.001,* CY1P0 vs P1 *P = 0.011*)

## Statistical Analyses

Survival analysis was done with Kaplan-Meier plots and compared with the log-rank test. All values are expressed as the means ± standard deviation with comparisons among the two or three groups made using the $\chi 2$ test and Student's $t$ test. Values of $P < 0.05$ were considered statistically significant. Statistical analysis was performed with SPSS Version 21.0 software program (SPSS Inc., Chicago, IL, USA).

# Results

## Clinicopathological Features and Clinical Results

We analyzed 115 patients (male 76, female 39) with advanced gastric cancer (large type 3, type 4, serosa-invasion) who underwent SL. Patients were classified into the CY0P0 group ($n = 56$), the CY1P0 group ($n = 26$), and the P1 group ($n = 33$). They had no other non-curative factors except for peritoneal dissemination and positive peritoneal cytology. In clinicopathological features, among the three groups, there were no significant differences in age, gender, tumor location, macroscopic type, clinical T factor, and clinical N factor. However, there were significant differences in clinical M factor and clinical stage, because peritoneal dissemination in some patients was preoperatively detected on MDCT (clinical M, $P < 0.001$; clinical stage, $P < 0.001$, Table 1).

Median survival times (MSTs) were 42 months in the CY0P0 group, 21 months in the CY1P0 group, and 12 months in the P1 group. Patients in the CY1P0 and the P1 groups had significantly poorer prognosis than patients in the CY0P0 group, and patients in the P1 group had significantly poorer

**Table 2** Surgical and pathological findings of patients who underwent conversion therapy

| | $n = 17$ (%) |
|---|---|
| Degree of peritoneal metastasis | |
| CY1 | 12 (70.6) |
| P1 | 5 (29.4) |
| Operative procedure | |
| Total gastrectomy | 12 (70.6) |
| Distal gastrectomy | 5 (29.4) |
| Surgical approach | |
| Open | 16 (94.1) |
| Laparoscopic | 1 (5.9) |
| Combined resection | |
| Spleen | 9 (52.9) |
| Lymph node dissection | |
| D1, D1+ | 0 (0) |
| D2 | 17 (100) |
| Postoperative complications* | |
| Grade II | |
| Surgical-site infection | 1 (5.9) |
| Interstitial pneumonia | 1 (5.9) |
| Grade IIIa | |
| Intestinal obstruction | 1 (5.9) |
| 30/60 day mortality | 0 |
| Residual tumor status | |
| R0 (no residual tumor) | 17 (100) |
| R1 (microscopic residual tumor) / | 0 |
| R2 (macroscopic residual tumor) | |
| Pathological response (primary site) | |
| Grade 1a (viable tumor cells occupy ≧ 2/3 of tumorous area) | 3 (17.6) |
| Grade 1b (viable tumor cells occupy ≧ 1/3 of tumorous area) | 5 (29.4) |
| Grade 2 (viable tumor cells occupy < 1/3 of tumorous area) | 8 (47.1) |
| Grade 3 (no viable tumor) | 1 (5.9) |

*Clavien–Dindo classification

prognosis than patients in the CY1P0 group (CY0P0 vs CY1P0, $P = 0.038$; CY0P0 vs P1, $P < 0.001$; CY1P0 vs P1, $P = 0.011$) (Fig. 1).

## Characteristics of Patients Who Underwent Conversion Surgery

The characteristics of the 17 patients who underwent CS are shown in Table 2. In total, 12 patients (70.6%) were in the CY1P0 group, and five patients (29.4%) were in the P1 group. Total gastrectomy was performed in 12 patients (70.6%), splenectomy was performed in nine patients (52.9%), and all patients underwent D2 lymph node dissection. Regarding postoperative complications, surgical-site infection and interstitial pneumonia each occurred in one patient (5.9%), who was treated conservatively (grade II). Intestinal obstruction (grade IIIa) occurred in one patient (5.9%). There was no mortality. R0 resection was achieved in all patients, and grade 2 and 3 histological responses of the resected primary tumor were obtained in 8 (47.1%) and 1 (5.9%) patient(s), respectively. After surgery, 14 patients (82.4%) received adjuvant chemotherapy with S-1 agent; the one-year completion rate was 57.1% (8/14). Of 17 patients who underwent CS, 10 patients died. The causes of death were peritoneal metastasis ($n = 9$) and paraaortic lymph node metastasis ($n = 1$).

## Clinicopathological Characteristics and Survival of Patients in the CY1P0 Group

Regarding clinical course of 26 patients with CY1P0, 24 patients received chemotherapy, and two other patients underwent non-curative gastrectomy, one for bleeding

**Table 3** Characteristics of 26 patients with CY1P0

| Variable | Conversion surgery (+) ($n = 12$) | Conversion surgery (−) ($n = 14$) | $p$ |
|---|---|---|---|
| Gender (male/female) | 8/4 | 8/6 | 0.795 |
| Age (range) | 69 (49–75) | 66 (43–72) | 0.371 |
| Tumor location (U,M, L/whole) | 6/6 | 7/7 | 1.00 |
| Macroscopic type (Well/ Ill-definded) | 0/12 | 1/13 | 0.328 |
| Characteristic of tumor (type4/large type3/other serous invasion) | 9/3/0 | 9/4/1 | 0.619 |
| Clinical T (3/ 4a/ 4b) | 0/12/0 | 1/12/1 | 0.366 |
| Clinical N (0/ 1,2,3) | 2/10 | 2/12 | 0.924 |
| Clinical Stage (II/ III) | 2/10 | 2/12 | 0.924 |
| Clinical Response of primary lesion (PR,MR/ SD,PD) | 10/2 | 5/9 | 0.019 |
| Ascites (Positive/Negative) | 2/10 | 8/6 | 0.049 |
| Preoperative serum CEA (ng/mL [range]) | 1.9 (0.5–5.4) | 4.1 (0.1–46.8) | 0.056 |
| Preoperative serum CA19–9 (ng/mL [range]) | 8.9 (2–1108.8) | 8.6 (1.7–1890.5) | 0.528 |
| Courses of chemotherapy (≧5/ ≦4) | 8/4 | 4/10 | 0.049 |
| Histological type (Well-differentiated/ Undifferentiated) | 3/9 | 3/11 | 0.538 |

*PR* partial response, *MR* minor response, *NC* no change, *PD* progressive disease

and the other for gastric outlet obstruction. Among the 24 patients who received chemotherapy, 18 patients underwent second-look SL, one patient underwent non-curative gastrectomy due to bleeding during chemotherapy, and five patients changed to another chemotherapeutic regimen due to progressive disease. Among the 18 patients who underwent second-look SL, 12 patients underwent CS (R0) because peritoneal cytology turned negative, and six patients changed to another chemotherapeutic regimen because peritoneal cytology was positive. Five of these six patients had partial response (PR) or minor response (MR) to chemotherapy. The rate of negative conversion in peritoneal cytology was 66.7% (12/18). These regimens of chemotherapy were S-1/CDDP ($n = 9$), Docetaxel/CDDP/S-1 ($n = 2$), and S-1/Docetaxel ($n = 1$), and the median number of treatment courses before surgery was five.

**Table 4** Independent predictors of overall survival among patients with CY1P0

| Factors | $n$ | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | $p$ | HR | 95% CI | $p$ |
| CS | | | | | | | |
| No | 14 | 1 | | | 1 | | |
| Yes | 12 | 0.091 | 0.019–0.448 | 0.003 | 0.118 | 0.020–0.699 | 0.019 |
| Chemotherapy (cycles) | | | | | | | |
| 4≧ | 14 | 1 | | | 1 | | |
| 5≦ | 12 | 0.232 | 0.073–0.738 | 0.013 | 0.285 | 0.078–1.033 | 0.056 |
| Preoperative CEA | | | | | | | |
| 2.6 > | 13 | 1 | | | 1 | | |
| 2.6 < | 13 | 1.060 | 1.020–1.101 | 0.003 | 1.034 | 0.994–1.075 | 0.094 |

*CS* conversion surgery, *HR* hazard ratio, *CI* confidence interval

In characteristics of 26 patients with CY1P0, there were no significant differences of age, gender, tumor location, macroscopic type and characteristics of tumor, clinical T factor, clinical N factor, or clinical stage between the CS group and the non-CS group (Table 3). However, the frequency of PR or MR to chemotherapy, preoperative negative ascites, and the frequency of more than five courses of chemotherapy were significantly higher in the CS group than in the non-CS group (clinical response $P = 0.019$, Ascites $P = 0.049$, courses of chemotherapy $P = 0.049$) (Table 3).

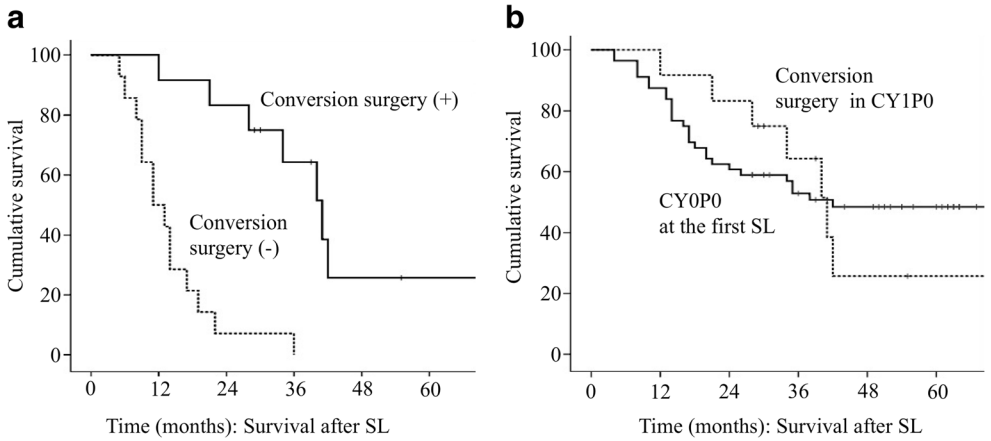


**Fig. 2** **a** Overall survival curves of 26 patients in the CY1P0 group after SL between the conversion surgery (CS) group (——) and the non-CS group (– – – –). MSTs of patients with and without CS were 41 and 11 months, respectively (median follow-up 19 (5–82) months) ($P < 0.001$). **b** Overall survival curves of patients who underwent CS in the CY1P0 group and those in the CY0P0 group at first SL. MSTs of patients with CS in the CY1P0 group (– – – –) and those in the CY0P0 group at the first SL (——) were 41 and 42 months, respectively (median follow-up 34 (4–82) months) ($P = 0.913$)

The predictors of a favorable overall survival among patients with CY1P0 were CS, more than five courses of chemotherapy and preoperative low CEA value (Table 4). The only independent predictor of overall survival was CS (Table 4).

MSTs of patients with or without CS were 41 and 11 months, respectively, and the survival of patients with CS was significantly longer than that without CS ($P < 0.001$) (Fig. 2a). Regarding overall survival of patients with CS in the CY1P0 group or patients in the CY0P0 group at first SL, there were no differences in overall survival between two groups ($P = 0.913$) (Fig. 2b).

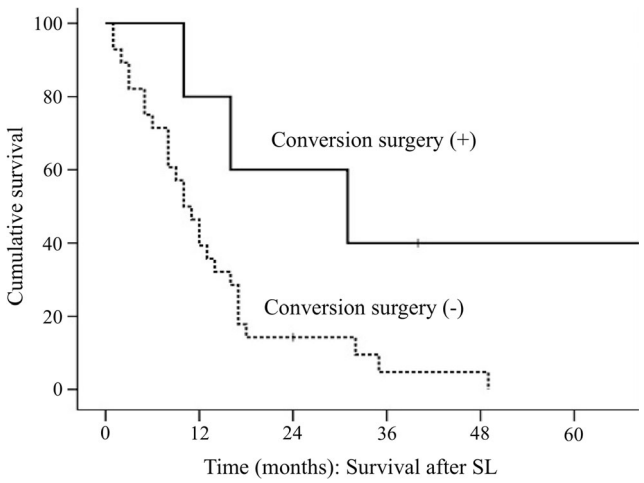


**Fig. 3** Overall survival curves of 33 patients in the P1 group after SL between CS group (——) and the non-CS group (– – – –). MSTs were 31 months in the CS group and 10 months in the non-CS group (median follow-up 12 (1–69) months) ($P = 0.034$)

## Clinicopathological Characteristics and Survival of Patients in P1 Group

Regarding the clinical course of 33 patients with P1, all patients with P1 received chemotherapy, seven patients underwent second-look SL. Five of these seven patients underwent CS (R0) because peritoneal dissemination disappeared by chemotherapy, and two patients changed to another chemotherapeutic regimen because peritoneal dissemination remained. The rate of negative conversion in peritoneal dissemination was 15.2%.

In clinicopathological features of R0 cases in P1, 80% of all patients received five courses of chemotherapy (data not shown). One patient had grade 3 in pathological response, their relapse-free survival time was 43 months, and overall survival was 69 months. Regarding overall survival of patients with or without CS in the P1 group, MSTs were 31 months in the CS group and 10 months in the non-CS group, and survival was significantly longer in the CS group than in the non-CS group ($P = 0.034$) (Fig. 3).

## Discussion

Recently, CS for gastric cancer has attracted significant attention as an advanced therapeutic strategy.[17] Though some previous studies have evaluated the significance of CS or salvage surgery after chemotherapy in advanced gastric cancer patients,[30,31] there is insufficient evidence on whether CS can produce meaningful survival benefits for patients with peritoneal metastasis. The present study suggests that CS has clinical safety and efficacy for gastric cancer patients with peritoneal metastasis. Regarding overall survival of patients

with CS in CY1P0 or CY0P0 at first SL, there were no differences in overall survival between the two groups. We therefore demonstrated that CS could contribute to improvement of survival of patients with negative conversion in peritoneal metastasis. Some reports have showed that the curative resection (R0) resulted in long-term survival, and microscopic residual tumors (R1) and macroscopic residual tumors (R2) were strong prognostic factors for surgery for unresectable metastatic gastric cancer.[18,32,33] Moreover, regarding the palliative resection of the primary tumor, the REGATTA trial showed that the treatment strategy of non-curative gastrectomy followed by chemotherapy failed to provide a survival advantage compared with chemotherapy alone.[34] Therefore, our rationale for CS is to perform curative resection (R0) when peritoneal metastasis disappears, which might lead to prolongation of survival.

Assessment of the responses to chemotherapy for diffusely disseminated and unmeasurable peritoneal lesions is extremely difficult. We used SL to confirm the degree of the peritoneal metastasis after systemic chemotherapy. In the present study, total 200 mL of saline was used for peritoneal cytology during SL, and the false-negative rate of CY1 or P1 was 0%. Therefore, second-look SL is the less invasive and more useful evaluation method. We propose that the best timing for the operation might be at the point when negative conversion of CY1 and P1 is detected based on the diagnosis of second SL.

Other issues should be discussed in order to establish the concept for CS, including the optimal number of chemotherapeutic courses, the optimal chemotherapy regimen, and predictive factors for CS. We showed that the frequency of more than five courses of chemotherapy was higher in the CS group than in the non-CS group of patients with CY1P0, and 80% of all patients who underwent CS in the P1 group received five courses of chemotherapy. We therefore estimate more than five courses of chemotherapy might be essential to get negative conversion in peritoneal cytology and peritoneal dissemination.

The regimen of chemotherapy before surgery is another noteworthy issue. We have used S-1 base regimens such as S-1/CDDP, Docetaxel/CDDP/S-1, and S-1/docetaxel. Regarding the response rate in patients with CY1P0, there were no significant differences between the three types of chemotherapy (S-1/CDDP 61.1% [11/18], Docetaxel/CDDP/S-1 66.7% [2/3], S-1/docetaxel 66.7% [2/3]). The rates of negative conversion in CY1 or P1 were 66.7 and 15.2% respectively. In order to further improve the curability, a powerful and effective regimen is necessary for patients with peritoneal metastasis. Combination therapy with nanoparticle albumin-bound PTX (Nab-PTX) or molecular targeting agents, which could target peritoneal dissemination in the gastric cancer, might induce a higher conversion rate with high R0 rate than previous agents.[35]

It is necessary to analyze the predictive factors for CS, and the effective biomarker to expect response of chemotherapy. We showed that effective clinical response such as partial response (PR) or minor response (MR) to chemotherapy was significantly higher in the CS group than in the non-CS group. Moreover, in the P1 group, one patient who showed the Grade 3 status in pathological response to chemotherapy had long-term survival after CS. Effective clinical response might therefore reflect negative conversion in peritoneal metastasis, and CS might be significantly valuable for survival of patients with effective pathological response by chemotherapy.

The timing of performance of when the second-look laparoscopy should be performed is another important issue. We showed that more than five courses of chemotherapy and effective clinical response for chemotherapy might be essential to get negative conversion in peritoneal cytology and peritoneal dissemination. We therefore propose that second-look laparoscopy should be performed when effective clinical response is recognized after more than five courses of chemotherapy.

There are several limitations to this study. As it is a small-scale study, a prospective randomized controlled trial or a large cohort study will help to further determine whether CS leads to a better prognosis, and clarify the therapeutic usefulness of CS using assessment of second-look SL. Some problems remain necessary to be overcome regarding the chemotherapy regimen before CS, the timing of CS, and the postoperative chemotherapy regimen. Moreover, discovering reliable biomarkers that reflect survival benefit is strongly desirable in future studies.

In conclusion, this study suggests that conversion surgery is probably safe and may contribute to improve the survival rate of patients with peritoneal dissemination or positive peritoneal cytology findings.

**Author Contributions** Study concept and design: Nakamura and Yamaue
Acquisition of data: Nakamura, Ojima, Nakamori, Katsuda, Tsuji, Hayata, and Kato
Analysis and interpretation: Nakamura, Ojima, Nakamori, and Tsuji
Drafting of the manuscript: Nakamura, Ojima, Katsuda, and Tsuji
Critical revision of the manuscript for important intellectual content: Nakamori, Yamaue, Hayata, and Kato
Administrative, technical, and material support: Ojima, Nakamori, and Yamaue
Study supervision: Yamaue

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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