induced stromal changes occur regardless of the tumor response.

The radiologic N and pathologic N stages were significantly correlated even though the radiologic overall accuracy of N-staging was only 44%. Moreover, the radiologic accuracy and sensitivity of the diagnosis of nodal positivity were both high: 70.7 and 84.9%, respectively. These results suggest that N-staging using CT is not accurate for diagnosing each N category, although it is useful for diagnosing nodal positivity. Previously, Park et al. [13] reported that the accuracy of N restaging was 39% on EUS and 37% on CT, whereas that of nodal positivity was 68% on both EUS and CT in 38 patients. Their results support our data. The sensitivity for diagnosing nodal positivity in this study was high, at 84.9%; however, the specificity was low, at 36.4%, thus suggesting that radiologically determined positive findings are reliable, whereas negative findings are not.

We next examined the accuracy of N-staging by stratifying the radiologic nodal response. The radiologic accuracy was low, at 39.3%, in the responders and higher, at 52.1%, in the nonresponders, which suggests that the radiologic accuracy of N-staging decreases when metastatic nodes respond to chemotherapy. The rates of underdiagnosis and overdiagnosis were almost half in the overall cohort and the nonresponders; however, overdiagnosis was a major cause of misdiagnosis in the responders. Among the responders, eight (89%) of nine patients with pathologic N0 disease were radiologically misdiagnosed as being node-positive. This result suggests that the enlarged nodes did not disappear even though the nodal metastasis pathologically disappeared.

In conclusion, restaging of gastric cancer after neoadjuvant chemotherapy by using CT is inaccurate and unreliable. In particular, the radiologic T stage determined after neoadjuvant chemotherapy should not be considered in clinical decision-making.

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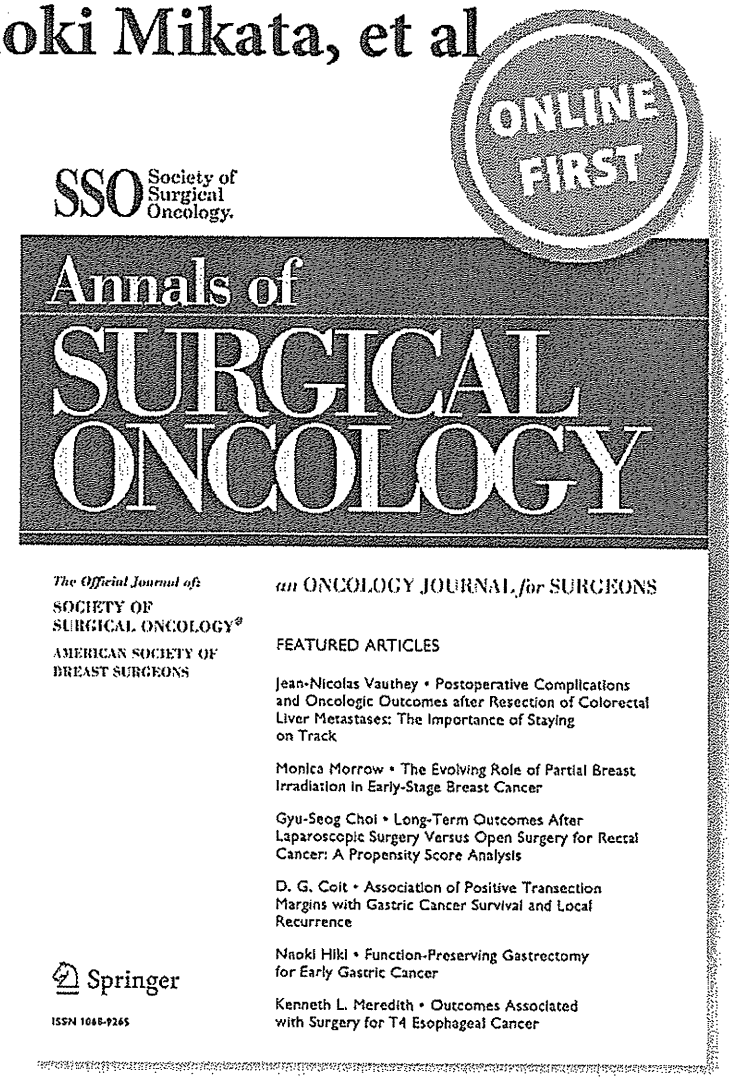

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Induction of a Pathological Complete Response by Four Courses of Neoadjuvant Chemotherapy for Gastric Cancer: Early Results of the Randomized Phase II COMPASS Trial

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ABSTRACT

Background. The prognosis for stage 3 gastric cancer is not satisfactory, even with S-1 adjuvant chemotherapy. A randomized phase II trial was conducted to compare two and four courses of neoadjuvant S-1/cisplatin (SC) and paclitaxel/cisplatin (PC) using a two-by-two factorial design for locally advanced gastric cancer. The primary endpoint was overall survival. We clarified the impact of these regimens on the secondary endpoints, including the clinical and pathological responses, chemotherapy-related toxicities, and surgical results.

Methods. Patients received S-1 (80 mg/m^2 for 21 days with 1 week's rest)/cisplatin (60 mg/m^2 at day 8) or paclitaxel/cisplatin (80 and 25 mg/m^2, respectively, on days 1, 8, and 15 with 1 week's rest) as neoadjuvant chemotherapy.

Results. Eighty-three patients were assigned to arm A (two courses of SC, $n = 21$), arm B (four courses of SC, $n = 20$), arm C (two courses of PC, $n = 21$), and arm D (four courses of PC, $n = 21$). Pathological response rate was 43 % in arm A, 40 % in arm B, 29 % in arm C, and 38 % in arm D. Pathological complete response was only observed in arms B (10 %) and D (10 %). Most bone marrow toxicities, nausea, vomiting, alopecia, and fatigue were slightly higher but acceptable in arms B and D. Grade 3/4 surgical morbidities were not commonly observed in all four arms.

Conclusions. Pathological complete response could be induced by four courses of neoadjuvant chemotherapy without a marked increase of toxicities, regardless of a SC or PC regimen.

Gastric cancer remains the second leading cause of cancer death worldwide.[1] For locally advanced disease, the standard treatment is chemotherapy and D2 gastrectomy in Asia, D2 plus postoperative chemotherapy with S-1 for 1 year in Japan, and D2 plus postoperative chemotherapy with capecitabine and oxaliplatin for around 6 months in Korea.[2–5] However, even with D2 gastrectomy and

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adjuvant chemotherapy with S-1, the prognosis of stage 3 tumors is not satisfactory.[6] In contrast to the use of adjuvant S-1 chemotherapy for 1 year in Japan, other approaches have been established in Western countries. Pre- and postoperative chemotherapy is a standard treatment in Europe.[7–9] Pre- or postoperative chemoradiation with D2 is frequently selected in the United States.[10]

Combination chemotherapy using S-1 plus cisplatin (SC) is a standard regimen administered for metastatic gastric cancer in Japan.[3,11] However, SC was not tolerable when it was started just after surgery, but was feasible and safe when provided preoperatively.[12–16] Paclitaxel is another key drug used for metastatic disease and has been tested in an adjuvant setting in a phase III trial.[17–19] Moreover, paclitaxel plus cisplatin (PC) demonstrated a high response rate and feasibility for metastatic disease.[17,20] Furthermore, PC achieved a high pathological response rate with acceptable toxicity in the neoadjuvant setting.[21] Both SC and PC are promising regimens for neoadjuvant chemotherapy; however, a suitable duration of treatment has not yet been established. Two courses have been selected in most Japanese studies, while three courses were adopted in the MAGIC phase III trial, which confirmed its survival benefit.[7,14,22] In contrast to neoadjuvant chemotherapy, the patients received S-1 for 1 year or capecitabine plus oxaliplatin for 6 months in the postoperative adjuvant setting after undergoing D2 gastrectomy.[4,5]

On the basis of these previous studies, a randomized phase II trial was conducted to compare neoadjuvant chemotherapy using two and four courses of SC and PC with a two-by-two factorial design for macroscopically resectable locally advanced gastric cancer.[23] The primary endpoint was overall survival (OS). The present study was a randomized phase II trial, which aimed not to draw definite conclusion but to select better regimen and course for the next phase III trial. This report clarified the impact of these regimens on early endpoints, including the clinical and pathological responses, chemotherapy-related toxicities, and surgical results.

PATIENTS AND METHODS

Eligibility Criteria

The eligibility criteria were as follows: (1) histologically proven gastric adenocarcinoma, (2) T2–3/N+ or T4aN0 in case of scirrhous or junctional tumors, T2–3 with nodal metastasis to the major branched artery, T4aN+ , T4b, paraaortic nodal metastases, or resectable minimal peritoneal metastases confirmed by laparoscopy, (3) no other distant metastasis, (4) age between 20 and 80 years, (5) Eastern Cooperative Oncology Group performance status of 0 or 1, (6) no previous treatment, (7) sufficient organ functions (white blood cell count >4,000/mm^3 and <12,000/mm^3, neutrophil count >4,000/mm^3, hemoglobin >8.0 g/dl, platelet count >100,000/mm^3, GOT <100 IU, GPT <100 IU, total bilirubin <1.5 mg/dl, creatinine clearance >30 mg/dl/h according to measured value or Cockcroft–Gault formula, no ischemic change or ventricular arrhythmia by exercise ECG), and (8) written informed consent provided. The exclusion criteria were as follows: (1) serious comorbidities, (2) synchronous or metachronous cancer (synchronous multiple cancers in the stomach included), (3) acute inflammation, (4) systemic treatment with a corticosteroid, (5) hypersensitivity to Cremophor EL, (6) pregnant or breast-feeding women, or women who were contemplating pregnancy, (7) mental disorders, (8) medical history of allergy or hypersensitivity to any drugs, (9) history of alcoholic anaphylaxis, (10) peripheral neuropathy, and (11) patients judged to be inappropriate for the study by the physicians.

The clinical diagnosis of the T and N stages was basically determined by thin-slice CT or multidetector row CT following Habermann's method.[24] Briefly, T4a tumors were defined as transmural tumors with obvious blurring of at least one-third of the tumor extent, or wide reticular strands surrounding the outer border of the tumor. Regional lymph nodes were considered to be involved by metastases if they were larger than 8 mm in the short-axis diameter. Staging laparoscopy was mandatory to diagnose peritoneal metastasis. Our previous study demonstrated that the accuracy was 71.4 % for T staging and 75.9 % for N staging according to the same method and criteria.[25]

Preoperative Chemotherapy

In the SC regimen, S-1 was provided twice a day for a total of 80 mg/m^2 for the first 3 weeks of a 4-week cycle, and cisplatin was provided as an intravenous infusion of 60 mg/m^2 on day 8 of each cycle, as described previously.[11] In the PC regimen, paclitaxel 60 mg/m^2 and cisplatin 25 mg/m^2 were administered on days 1, 8, and 15 as one course, which was repeated every 4 weeks.[20] The dose modification criteria were based on the previous studies.[11,21] Neoadjuvant chemotherapy was discontinued if there was documented disease progression, unacceptable toxicity, or withdrawal of consent.

Surgery

During the 2–6 weeks after completion of the neoadjuvant chemotherapy or when the tumors progressed during the treatment, patients proceeded to surgery on the basis of the criteria defined by the protocol. After laparotomy, the resectability was evaluated. Intraperitoneal wash cytology was mandatory. R0 resection was aimed for by gastrectomy with standard D2 lymphadenectomy.[3] D3 dissection or

combined resection of a small part of the peritoneum or adjacent organs were permitted for curative intent. Depending on the location of the primary tumor, the surgeon performed either a total or distal subtotal gastrectomy. In total gastrectomy for proximal tumors, the spleen was removed in principle for splenic hilar lymphadenectomy.

After a macroscopic curative resection was achieved, the patients were strongly recommended to undergo postoperative chemotherapy using S-1 for more than 6 months until 12 months, as long as the tumors did not recur. Any adjuvant treatment other than S-1 was not permitted until a recurrence developed.

Registration and Randomization

Eligible patients were registered into the data center of this study and then randomized as follows: arm A, two courses of SC; arm B, four courses of SC; arm C, two courses of PC; and arm D, four courses of PC. Randomization was performed by a centralized dynamic method using the following factors: scirrhous type including giant type 3 (yes or no), tumor invasion of the esophagus (yes or no), clinical stage 2–3b or 4, creatinine clearance (<60 or ≥60 mg/m^2/min), and institution as balancing variables.

Study Design and Statistical Methods

The present study was an open-label, randomized phase II trial of selection design as proposed by Simon.[26] The primary endpoint was the 3-year OS rate. The early key secondary endpoints were the incidence of adverse events, pathological response rate, clinical response rate, and R0 resection rate. The sample size was calculated on the hypothesis that the 3-year OS rate was expected to be between 20 and 40 % for each reference arm of the two courses and SC regimen. When each test arm of four courses and PC regimen achieved 10 % improvement of the 3-year OS rate, the statistical power (selection probability) was calculated to be 0.81, 0.79, and 0.78 for a total sample size of 60, and it was calculated to be 0.85, 0.83, and 0.82 for a total sample size of 80. Considering these calculations, the number of patients to be accrued was set at 60–80 in total.

The progression of tumors was evaluated by the 7th edition of the International Union Against Cancer tumor, node, metastasis classification system.[27] The clinical response was evaluated by the first version of the Response Evaluation Criteria for Solid Tumors.[28] Surgical specimens were pathologically evaluated as grade 0 when there was no degeneration and/or necrosis within the tumor, grade 1a when the area was less than one-third of the tumor, grade 1b when the area was more than one-third and less than two-thirds, grade 2a when the area was more than two-thirds but tumor tissues were apparently remained, grade 2b when only minimal tumor cells remained, and grade 3 when there was no residual tumor.[3] Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). The severity of surgical morbidity was evaluated by the Clavien–Dindo classification.[29]

The protocol was approved by the institutional review boards/ethics committees of each participating institution. This trial was registered in the University Hospital Medical Information Network (UMIN) center (ID UMIN00000 2595).

RESULTS

Patients

Between October 2009 and July 2011, a total of 83 patients were assigned to arm A (two courses of SC, $n = 21$), arm B (four courses of SC, $n = 20$), arm C (two courses of PC, $n = 21$), and arm D (four courses of PC, $n = 21$). All patients were eligible and received neoadjuvant chemotherapy. Table 1 shows the patient demographics and tumor characteristics.

The actual courses were defined as one course when cisplatin (CDDP) was provided at least one time during one course. The rate of completion of neoadjuvant chemotherapy was 91 % (19 of 21) in arm A, 60 % (12 of 20) in arm B, 100 % (21 of 21) in arm C, and 81 % (17 of 21) in arm D. The rate of completion of chemotherapy was 76 % (31 of 41) in the SC arm compared to 90 % (38 of 42) in the PC arm, and 95 % (40 of 42) in the two-course arm compared to 71 % (29 of 41) in the four-course arm. A total of six patients did not proceed to surgery because of disease progression. Among the patients who proceeded to surgery, two patients in arm C received a bypass operation because of peritoneal metastasis. Five patients underwent an R2 resection because of peritoneal metastasis, and eight patients had an R1 resection as a result of positive peritoneal cytology. All patients without peritoneal metastasis and positive peritoneal cytology received a D2 gastrectomy. The R0 resection rate was 81 % (17 of 21) in arm A, 75 % (15 of 20) in arm B, 67 % (14 of 21) in arm C, and 76 % (16 of 21) in arm D. The R0 resection rate was 78 % (32 of 41) in the SC arm and 71 % (30 of 42) in the PC arm, while it was 74 % (31 of 42) in the patients treated with two courses and 76 % (31 of 41) in the patients treated with four courses. A flow diagram of the patients is provided in Supplementary Appendix Fig. A1.

TABLE 1 Patient characteristics

Characteristic	Variable	Arm A ($n = 21$)	Arm B ($n = 20$)	Arm C ($n = 21$)	Arm D ($n = 21$)
Age	Median	66	63	66	67
	Range	32–79	47–76	55–80	43–77
Gender	M/F	14/7	12/8	17/4	15/6
Performance status	0/1	21/0	20/0	20/1	20/1
Macroscopic type	Non-scirrhous	15	15	15	12
	Type 4/giant type 3	6	5	6	9
Histological type	Differentiated	8	9	11	8
	Undifferentiated	13	11	10	13
Clinical T	T2	0	0	0	1
	T3	1	1	2	2
	T4a	17	19	17	15
	T4b	3	0	2	3
Clinical N	N0	1	4	3	4
	N1	12	7	8	8
	N2	8	9	9	9
	N3	0	0	1	0
Clinical M	Negative	18	17	17	18
	Positive	3	3	4	4
Site of M	P or CY	3	3	3	4
	Para-aortic nodes	0	0	1	0

Response

Twenty-four patients had only nonmeasurable lesions and 59 had measurable lesions. The overall clinical response, evaluated among all 83 patients, was 43 % (9 of 21) in arm A, 50 % (10 of 20) in arm B, 24 % (5 of 21) in arm C, and 29 % (6 of 21) in arm D (Supplementary Appendix Table A1). The response rate was 46 % (19 of 41) in the SC arm and 26 % (11 of 42) in the PC arm, while it was 33 % (14 of 42) in the patients treated with two courses and 39 % (16 of 41) in those treated with four courses. The non-PD rate was 93 % (38 of 41) in the SC arm and 93 % (39 of 42) in the PC arm, while it was 95 % (39 of 41) in the patients treated with two courses and 90 % (38 of 42) in those treated with four courses.

Table 2 indicates the pathological response of the primary tumor. The pathological response rate, defined as tumor regression by more than two-thirds was 43 % (9 of 21) in arm A, 40 % (8 of 20) in arm B, 29 % (6 of 21) in arm C, and 38 % (8 of 21) in arm D. The pathological response rate was 42 % (17 of 41) in the SC arm and 33 % (14 of 42) in the PC arm, while it was 36 % (15 of 42) in the patients treated with two courses and 39 % (16 of 41) in those treated with four courses. The pathological complete response rate was 0 % (0 of 21) in arm A, 10 % (2 of 20) in arm B, 0 % (0 of 21) in arm C, and 10 % (2 of 21) in arm D. The pathological complete response rate was 0 % with a 95 % confidence interval from 0 to 8 % in the two-course arm and 10 % with a 95 % confidence interval from 3 to 23 % in the four-course arm. The P value for this comparison according to Fisher's exact test was 0.055. All patients who experienced pathological complete response had no tumor cells in either the primary tumor or the lymph nodes dissected. All patients who exhibited a pathological complete response completed four courses of chemotherapy.

Chemotherapy-Related Toxicities

The most frequently detected toxicities (all grades) in the SC arm were anemia in 33 patients (81 %), followed by neutropenia in 26 (63 %), appetite loss in 24 (59 %), leukocytopenia in 21 (51 %), fatigue in 15 (37 %), and nausea in 15 (37 %), while those in the PC arm were anemia in 37 patients (88 %), followed by leukocytopenia in 33 (79 %), nausea in 17 (41 %), alopecia in 14 (33 %), anorexia in 16 (38 %), and hyperkalemia in 16 (38 %). Most bone marrow toxicities, nausea, vomiting, alopecia, and fatigue were slightly higher, but still acceptable, in the four-course arms, regardless of the regimen. Grade 3/4 toxicities were not frequently observed for either the SC or PC regimen. Grade 3/4 nonhematological toxicities occurred in less than 10 % of patients in all arms (Supplementary Appendix Table A2).

TABLE 2 Pathological response of primary tumor

Characteristic	Arm A ($n = 21$)	Arm B ($n = 20$)	Arm C ($n = 21$)	Arm D ($n = 21$)
Grade 0	1	5	2	2
Grade 1a	10	5	10	9
Grade 1b	2	1	2	2
Grade 2a	5	3	4	4
Grade 2b	2	2	0	0
Grade 3	0	2	0	2
Unknown	0	0	0	0
Unresected	1	2	3	2

Surgery

Table 3 shows the details of the surgical procedure performed. Most patients received total gastrectomy and D2 dissection. More than half of the patients who received D2 total gastrectomy received splenectomy. D1 dissection was only selected when the patients had peritoneal metastasis or positive peritoneal cytology.

The surgical morbidity (all grade) is shown in Table 4. Grade 3 morbidities included anastomotic leakage, which occurred in 5 % of the patients in arms A and C, pancreatic fistula, abdominal abscess, and pyothorax, each of which occurred in 5 % of the patients in arm C, and postoperative hemorrhage in 6 % of the patients in arm B. Readmission was observed in one patient from arm C. None of the patients required reoperation. No surgical mortality was observed.

TABLE 3 Surgical findings

	Arm A	Arm B	Arm C	Arm D
Proceeded to surgery				
n	20	18	20	19
Bypass				
n	0	0	2	0
Gastrectomy				
Total	15	14	16	13
Distal	5	4	2	6
Dissection				
D1	2	2	2	0
D2	18	16	16	19
Combined organ resection				
Spleen	9	7	10	11
Gallbladder	1	4	4	2
Transverse colon	1	0	2	2
Pancreas	0	0	0	2
Diaphragm	0	1	1	0
Liver	0	1	0	0
Bleeding, g				
Median	365	470	468	320
Range	60–1280	0–1300	120–1560	70–1990
Time, min				
Median	256	239	253	254
Range	155–395	176–422	162–380	172–381

DISCUSSION

To our knowledge, the present study is the first randomized trial to compare the duration of neoadjuvant chemotherapy for locally advanced gastric cancer. The major finding of this study was that a high pathological complete response rate of 10 % was only achieved when four courses of neoadjuvant chemotherapy were completed. Although the comparison of the pathological complete response did not reach statistical significance, the result was highly suggestive because this trial was a randomized study and there was no bias in the background. So far, such a high pathological complete response rate has never been reported from any other studies using one, two, or three courses of neoadjuvant chemotherapy for gastric cancer.[7,9,14–16,22]

Even though the pathological response was almost equivalent between the two- and four-course arms, as well as between the SC and PC regimens, a pathological complete response was observed only in 10 % of the patients treated with four courses, regardless of the regimen. The patients were well randomized to each arm in terms of the background of the patients and tumor characteristics. The compliance with chemotherapy was similar in both the two- and four-course arms. Therefore, an accidental imbalance of patients, tumors, or chemotherapy could not explain the fact that this high pathological complete response was only observed in patients who received four courses of chemotherapy. These results indicated that a pathological complete response was induced by the addition of third and fourth courses. Previously, several investigators reported that the pathological response clearly separated the survival of gastric cancer patients who received neoadjuvant chemotherapy.[30,31] However, it was unclear whether the patients who experienced a pathological complete response had different survival from those who experienced a partial response. Our study will clarify the answer to this question in the future.

In contrast to the pathological response, only one patient (in arm B) exhibited a clinical complete response. A clinical complete response is a rare event in gastric cancer chemotherapy. Previously, a clinical complete response was reported in one of 87 metastatic gastric cancer patients who received SC and also in one of 49 metastatic patients who received a PC regimen.[11,20] The discrepancy between the pathological and clinical responses may be explained

TABLE 4 Surgical morbidity

Proceeded to surgery	Arm A ($n = 20$)		Arm B ($n = 18$)		Arm C ($n = 20$)		Arm D ($n = 19$)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Postoperative bleeding	2	0	1	1	1	0	0	0
Anastomotic leakage	1	1	0	0	2	1	0	0
Pancreas fistula	1	0	3	0	2	1	3	0
Abdominal abscess	1	0	0	0	2	1	0	0
Wound infection	0	0	0	0	0	0	0	0
Ileus	0	0	0	0	0	0	0	0
Anastomotic stenosis	0	0	1	0	0	0	0	0
Pneumonia	0	0	1	0	0	0	0	0
Pyothorax	0	0	0	0	1	1	0	0

by the difficulties in evaluating patients for a clinical complete response. The response of the primary tumor is hard to be evaluated clinically, as the primary tumor is generally a nonmeasurable lesion. In three patients who exhibited a pathological complete response of lymph nodes in this study, the lymph nodes that had been considered to be occupied by the tumor were replaced by connective tissue but were not reduced in size. This is the reason why these three patients were not diagnosed with a clinical complete response of lymph nodes.

The chemotherapy-related toxicities increased when patients were treated with four courses compared to two. Most bone marrow toxicities, nausea, vomiting, alopecia, and fatigue were more frequently observed in those provided four courses than in those provided two courses of therapy, regardless of the regimen. However, the grade 3/4 toxicities were acceptable in the four-course arms of both regimens. No chemotherapy-related death was observed. On the other hand, surgical morbidities were not frequently observed in all four arms. Moreover, grade 3/4 complications were rare. No surgical mortality was observed. Thus, the administration of four courses of a SC or PC regimen, followed by surgery, appears to be feasible and safe.

Another concern in the four-course arm is the loss of a chance to receive R0 resection as a result of tumor progression during long-term chemotherapy. In the present study, the R0 resection rate was not low in the four-course arm compared with that observed in the two-course arm. Moreover, no patients exhibited disease progression during the third or fourth courses of chemotherapy. Tumor progression was observed during the initial two courses only. Although the rate of completing neoadjuvant chemotherapy was slightly lower in the four-course arm than in the two-course arm, the substantial difference was interpreted to be due to the toxicities observed in a few patients during the third and fourth courses. These results strongly suggest that compliance with chemotherapy was similar between the two- and four-course arms. When comparing the SC and PC regimens as neoadjuvant chemotherapy, both the radiological and pathological response rates were slightly lower in the PC arm than in the SC arm. However, the rates of R0 resection and pathological complete response were almost equivalent. The chemotherapy-related toxicities were feasible and safe in both regimens. The surgical morbidity was also low regardless of the regimen. The long-term survival results of the present study will clarify which regimen is better for neoadjuvant chemotherapy for gastric cancer.

This study included patients with para-aortic nodal metastases or resectable minimal peritoneal metastases. Para-aortic nodal metastasis is classified as M1 but is curable with neoadjuvant chemotherapy and surgery. Two phase II trials of neoadjuvant chemotherapy clarified that a high 3-year survival rate was obtained with neoadjuvant chemotherapy: 27 % with two courses of CPT-11 plus CDDP and 58.8 % with two courses of S-1 plus CDDP.[22,32] On the other hand, a peritoneal lavage cytology positive (CY1) status is also classified as M1 and is also curable with surgery and adjuvant chemotherapy containing S-1. Kodera and coworkers[33] reported that a 2-year survival rate of 46 % was obtained with surgery and S-1 therapy in patients with CY1. Without staging laparoscopy, CY1 or minimally resectable peritoneal metastasis is treated as clinically resectable disease. From the viewpoint of the prognosis and treatment strategy, para-aortic nodal metastases or resectable minimal peritoneal metastases are similar candidates for a trial of neoadjuvant chemotherapy for locally resectable advanced M0 disease.

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ORIGINAL ARTICLE

Incidence of metachronous gastric cancer in the remnant stomach after synchronous multiple cancer surgery

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Abstract
Background In the preoperative evaluation for gastric cancer, high-resolution endoscopic technologies allow us to detect small accessory lesions. However, it is not known if the gastric remnant after partial gastrectomy for synchronous multiple gastric cancers has a greater risk for metachronous cancer. The purpose of this study was to determine the incidence of metachronous cancer in this patient subset compared with that after solitary cancer surgery.
Methods Data on a consecutive series of 1,281 patients gastrectomized for early gastric cancer from 1991 to 2007 were analyzed retrospectively. The 715 gastric remnants after distal gastrectomy were periodically surveyed by endoscopic examination in Shikoku Cancer Center. Among those surveyed cases, 642 patients were pathologically diagnosed with solitary lesion (SO group) and 73 patients with synchronous multiple lesions (MU group) at the time of the initial surgery.
Results In the follow-up period, 15 patients in the SO group and 3 patients in the MU group were diagnosed as having metachronous cancer in the gastric remnant. The cumulative 4-year incidence rate was 1.9 % in the SO group and 5.5 % in the MU group. The difference did not reach the significant level by the log-rank test.
Conclusions The incidence of metachronous cancer is higher after multiple cancer surgery; however, the difference is not statistically significant.

Keywords Distal gastrectomy · Gastric stump cancer · Early gastric cancer

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Introduction

Multiple gastric cancers have been known to arise in two different patterns: one is synchronous multiple cancers, and the other is metachronous secondary cancer, which develops after removal of the primary gastric cancer. When partial gastrectomy is performed for removal of the primary cancer, the metachronous cancer can be called remnant gastric cancer [1–4]. It has been reported that the incidence of metachronous gastric cancer after partial gastrectomy for early gastric cancer is 0.6–3.0 % [1, 4–6].

The incidence of synchronous multiple gastric cancers has been reported to occur in 5–8 % of surgically resected stomachs [7–11]. However, a comprehensive evaluation using serial sections of the whole stomach revealed that it was 13–15 % [10, 12], which suggests a higher incidence of latent lesions in the whole stomach [13]. If the latent lesion cannot be detected by preoperative examinations and is left in the gastric remnant, the lesion may arise as a metachronous cancer. In contrast, if the accessory lesion is located in the resected stomach, it can be pathologically diagnosed as a synchronous multiple cancer.

It has been reported that both metachronous and synchronous multiple gastric cancers are thought to derive from multicentric carcinogenesis and have similar characteristics [10, 14]. However, it is not known if the gastric remnant after partial gastrectomy for synchronous multiple

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cancer is at greater risk for metachronous cancer. If this is the case, an intensive postoperative endoscopy surveillance program should be implemented for this patient group to detect metachronous cancer at its early and curable stage.

There have been few reports comparing the incidence of metachronous cancer in the gastric remnant after partial gastrectomy for solitary and multiple gastric cancers [11, 15, 16]. Because these reports differ in their conclusions, it remains controversial whether it is higher after multiple cancer surgery. The purpose of this study was to clarify the incidence of metachronous cancer in the gastric remnant after synchronous multiple cancer surgery compared with solitary cancer surgery. For this study, we chose distal gastrectomy as the partial gastrectomy technique because it is the most common surgical treatment for gastric cancer [17, 18].

Patients and methods

A retrospective database review of a consecutive series of 1,281 cases of gastrectomy for pathologically confirmed early gastric cancer from 1991 to 2007 in Shikoku Cancer Center identified 910 patients who underwent distal gastrectomy (Fig. 1). Negative surgical margin was confirmed by pathological examination in the resected specimens of all these patients. Following surgery, it was recommended that patients undergo surveillance endoscopic examinations at short intervals, annually, if possible, or every 2–3 years as the maximum interval. Among the afore-described patients, 715 patients underwent such endoscopic examinations in Shikoku Cancer Center with a follow-up time of more than 1 year after the surgery and were included in this study.

Early gastric cancer, defined as that invading the mucosal or submucosal layer regardless of lymph node metastasis, was classified according to the Japanese classification of gastric carcinoma [19]. The resected stomachs were processed in the usual manner. Briefly, resected stomachs were opened along the greater curvature, placed on a wooden board with the mucosa facing up, and fixed with a 10 % formalin solution for at least 24 h. Several portions, including the distal and proximal stump as well as both main and sublesions, were sliced to a thickness of 5 mm and histologically examined. For exploration of multiple lesions, resected specimens were macroscopically evaluated before and after fixation, along with preoperative evaluation, using endoscopy and upper gastrointestinal studies.

Synchronous multiple gastric cancers were defined according to the criteria reported by Moertel et al. [20]., which are as follows: (1) each lesion is histologically malignant, (2) each lesion is separated from another by the normal gastric tissue, and (3) each lesion is not the result of a local extension or metastasis of another lesion. If the depth of cancer infiltration is the same in two or more lesions, the one extending over the greatest area is regarded as the main lesion, and the other lesions are regarded as accessory lesions.

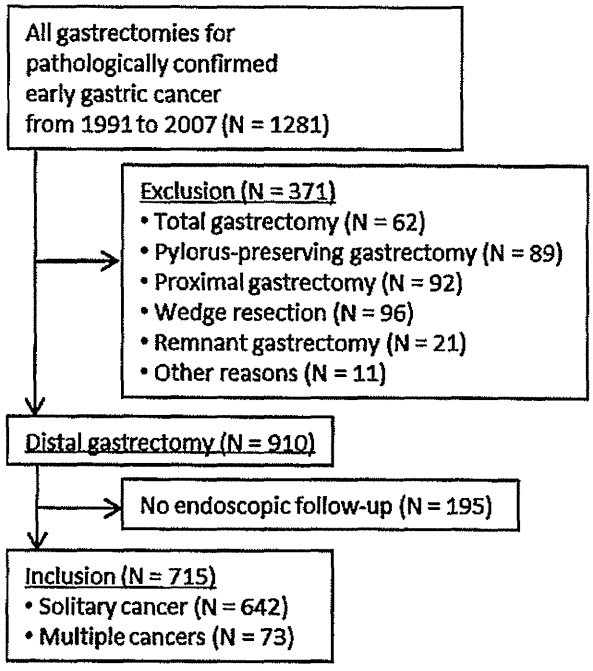

Fig. 1 Selection criteria for patients in this study. A consecutive series of 1,281 gastrectomies for pathologically confirmed early gastric cancer from 1991 to 2007 was retrospectively analyzed. Of these 910 patients who underwent distal gastrectomy, 715 had periodic endoscopic surveillance in Shikoku Cancer Center and were included in this study

Metachronous gastric cancer was defined using the following criteria [4]: first, that curative surgery of the initial cancers had been carried out with adequate surgical margins (5 mm or more); second, that the secondary cancers were found distant from the site of the anastomosis or the suture line to exclude recurrent tumors; third, that the secondary cancers were detected by endoscopic examinations more than 1 year after the gastrectomy. For all the surveillance endoscopic examinations, careful observation was made of the mucosa of the gastric remnant. Any suspicious lesions were biopsied and examined histologically. Follow-up time was defined as the period from the gastrectomy until the detection of metachronous gastric cancer by endoscopic examination or until the last endoscopic follow-up, at which point data were censored.

Details of distal gastrectomy are described in the Japanese gastric cancer treatment guidelines [17]. The JMP 9 statistical software (SAS Institute, Cary, NC, USA) was used for all statistical analysis. The cumulative prevalence rate of metachronous gastric cancer was calculated by the Kaplan–Meier method and analyzed by the log-rank test.

Pearson's chi-square test or Wilcoxon test was used to compare the two groups. The level of significance was set at $p < 0.05$.

Results

Data on a consecutive series of 1,281 gastrectomized patients for early gastric cancer from 1991 to 2007 were analyzed retrospectively (Fig. 1). The 715 gastric remnants after distal gastrectomy were periodically surveyed by endoscopic examination in Shikoku Cancer Center and were included in this study. Among those surveyed cases, 642 were pathologically diagnosed with solitary lesions (SO group) and 73 with multiple lesions (MU group) at the time of the initial surgery.

The clinicopathological characteristics of the two groups at the time of the initial surgery are shown in Table 1. Patients in the MU group were significantly older and were more likely to have intestinal-type cancer upon histological examination. Although the MU group contained more male cases and more protruded tumors, these differences did not reach a significant level. The tumors of both groups were mainly located in the middle or lower third of the stomach because the patients underwent distal gastrectomy. We did not observe any significant difference in tumor size, tumor depth, node metastasis, and lymphovascular invasion between the two groups.

In the MU group, 65 patients had two lesions, 7 had three lesions, and 1 had four lesions. The median diameter of the accessory largest lesions was 7 mm (Table 2). Most accessory lesions were intramucosal and of the intestinal histological type. The accessory lesions were also located in the middle or lower third of the stomach.

The median follow-up time from gastrectomy to the last surveillance endoscopy was 50 months (range, 12–193 months) in the SO group and 50 months (range, 12–216 months) in the MU group. In the follow-up period, 15 patients in the SO group and 3 patients in the MU group were diagnosed as having metachronous cancer in the gastric remnant. The median follow-up period of the 18 patients from initial surgery to the detection of metachronous cancer was 37 months (range, 13–149 months). They underwent curative resections by remnant gastrectomy ($n = 8$ patients) or endoscopic mucosal resection ($n = 10$ patients). The reconstruction method after distal gastrectomy in this study included Billroth I anastomosis ($n = 617$ patients), Billroth II anastomosis ($n = 19$ patients), and Roux-en-Y anastomosis ($n = 79$ patients). Metachronous gastric cancers arose in the gastric remnant in 15 patients after Billroth I anastomosis (2.4 %), in no patient after Billroth II anastomosis (0 %), and in 3 patients after Roux-en-Y anastomosis (3.8 %). There was no

Table 1 Clinicopathological characteristics at time of initial surgery

Factors	Solitary (642)	Multiple (73)	p value
Sex			
Male	410 (65 %)	53 (73 %)	0.139[c]
Female	232 (35 %)	20 (27 %)	
Age (years)			
Median (range)	64 (20–88)	68 (35–88)	<0.001[d]
Tumor location[a]			
Upper	12 (2 %)	0 (0 %)	0.477[c]
Middle	374 (58 %)	42 (58 %)	
Lower	256 (40 %)	31 (42 %)	
Macroscopic type[a,b]			
Protruded	126 (20 %)	20 (27 %)	0.140[c]
Depressed	495 (77 %)	52 (71 %)	
Tumor size (mm)[a]			
Median (range)	30 (2–150)	32 (5–115)	0.221[d]
Histological type[a]			
Intestinal	353 (55 %)	52 (71 %)	0.008[c]
Diffuse	289 (45 %)	21 (29 %)	
Depth of invasion[a]			
Mucosa	345 (54 %)	45 (62 %)	0.199[c]
Submucosa	297 (46 %)	28 (38 %)	
Node metastasis			
Negative	562 (88 %)	64 (88 %)	0.974[c]
Positive	80 (12 %)	9 (12 %)	
Lymphovascular invasion[a]			
Negative	473 (74 %)	57 (78 %)	0.415[c]
Positive	169 (26 %)	16 (22 %)	

[a] Status of the main lesion in the multiple group

[b] Flat type was included in the protruded type

[c] Pearson's chi-square test

[d] Wilcoxon test

Table 2 Clinicopathological characteristics of accessory lesion

Factors	Total[a] (73)
Tumor size (mm)	
Median (range)	7 (1–86)
Histological type	
Intestinal	59 (81 %)
Diffuse	14 (19 %)
Depth of invasion	
Mucosa	68 (93 %)
Submucosa	5 (7 %)
Tumor location	
Upper	1 (1 %)
Middle	35 (48 %)
Lower	37 (51 %)

[a] Status of largest tumor if patient has multiple accessory lesions

Table 3 Clinicopathological characteristics of metachronous cancer

Factors	Total (18)
Sex	
Male	16 (89 %)
Female	2 (11 %)
Age (years)[a]	
Median (range)	70 (57–82)
Tumor size (mm)	
Median (range)	13 (5–51)
Histological type	
Intestinal	14 (78 %)
Diffuse	4 (22 %)
Depth of invasion	
T1	16 (88 %)
T2	1 (6 %)
T3	1 (6 %)
Node metastasis[b]	
Negative	8 (100 %)
Positive	0 (0 %)

[a] Age at second treatment

[b] Status of gastrectomized cases only

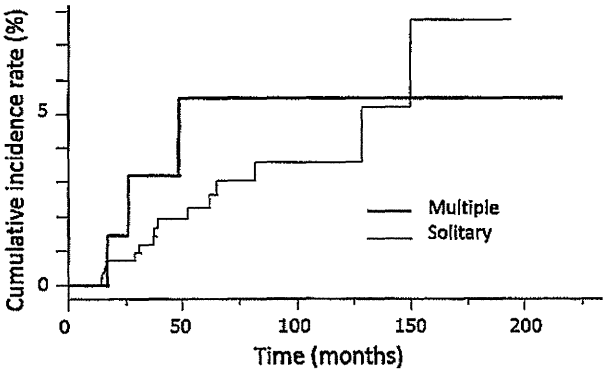

Fig. 2 Kaplan–Meier estimates of cumulative incidence of metachronous cancer in the gastric remnant. *Thin line* indicates the SO (solitary lesion) group; *bold line* indicates the MU (synchronous multiple lesions) group. There is no significant difference between the two groups by the log-rank test ($p = 0.454$)

statistically significant difference in the prevalence rate among these three groups.

Table 3 shows the clinicopathological characteristics of all 18 metachronous gastric cancers. Histologically, the dominant tumor type among these secondary cancers was the intestinal type. The majority of these patients had early stage T1 tumors ($n = 16$ patients), the remainder having T2 or T3 advanced tumors ($n = 2$ patients). Pathological lymph node metastasis was not found in any patients who underwent remnant gastrectomies. The cumulative 4-year incidence rate was 1.9 % in the SO group and 5.5 % in the MU group (Fig. 2). There was no significant difference between the two groups by the log-rank test ($p = 0.454$).

Discussion

The characteristics of synchronous multiple gastric cancers have been well studied [7, 9–12, 14, 21–23]: patients with synchronous multiple gastric cancers were more likely to be male and older and more likely to have the intestinal type of early gastric cancer. These characteristics were also observed in our current study (Table 1). With regard to tumor location, it has been known that multiple gastric cancers arise more frequently in the middle and lower than in the upper third of the stomach [9–11, 21, 23]. In addition, during whole stomach endoscopic surveillance after endoscopic mucosal resection for early cancer, the incidence rate of metachronous cancer in the upper, middle, and lower third of the stomach has been reported to be 17, 33, and 50 %, respectively [24]. These results suggest that the middle and lower third of the stomach have foci of multicentric carcinogenesis more than the upper third of the stomach. If distal gastrectomy is performed to remove the middle and lower third of the stomach, a very low incidence rate of the metachronous cancer is expected in the proximal gastric remnant. In other words, distal gastrectomy removes most of the foci of multicentric carcinogenesis from the whole stomach and reduces the incidence of metachronous cancer. We speculate that this is why the gastric remnant in the MU group failed to show a significantly greater risk for metachronous cancer in this study.

It has been well known that *Helicobacter pylori* infection in the gastric remnant after gastrectomy is associated with metachronous gastric cancer [25–27]. Now, *Helicobacter pylori* eradication is considered preventative therapy for metachronous gastric cancer [25, 28, 29]. In this study, the presence of *Helicobacter pylori* infection was confirmed at the time of the first surgery in 13 of 18 patients who developed metachronous gastric cancer. Because none of the patients received *Helicobacter pylori* eradication therapy after the first surgery, the infection remained in the remnant stomach in 10 of the 13 patients at the time of the second treatment. Therefore, among the metachronous gastric cancer subset, the *Helicobacter pylori* infection rate was 72 % at the time of the first surgery and 56 % in the gastric remnant. Because the median age of this patient group was 70 years, these infection rates were not very high [22, 30, 31]. However, *Helicobacter pylori* infection in this subset may be associated with the incidence of metachronous cancer.

It has been reported that Billroth II anastomosis is associated with gastric remnant cancer after distal gastrectomy for peptic ulcer because of duodenogastric reflux [32, 33]. In this study, the incidence rates of

metachronous gastric cancers after Billroth I anastomosis, Billroth II anastomosis, and Roux-en-Y anastomosis were 2.4, 0, and 3.8 %, respectively. The incidence rate after Billroth II anastomosis was even lower than the others. We speculate that this is because the duodenogastric reflux after Billroth II anastomosis induces the primary gastric remnant cancer in the long term after benign gastric ulcer surgery, but does not induce secondary metachronous cancer in the gastric remnant after early gastric cancer surgery [33].

Fujita et al. [11] have reported that the gastric remnant after synchronous multiple cancer surgery has a higher risk of metachronous cancer. They also have reported that a combination of diffuse-type synchronous multiple cancers at the time of the initial surgery was a potential risk factor for metachronous cancer in the gastric remnant [34]. However, in our current study, all three patients in the multiple group who developed metachronous cancer had a combination of intestinal-type synchronous multiple cancers at the time of the initial surgery. Limitations of this study are the relatively small number of patients and the relatively few events in the MU group. Therefore, we need to increase the study size to further clarify a risk factor for metachronous cancer in future.

We have previously reported that male gender, elder age, submucosal invasion, and proximal gastrectomy at the time of the first surgery were independent risk factors for the metachronous cancer after early cancer surgery [4]. In that report, we recommended yearly or biyearly surveillance endoscopy for patients with any of these risk factors and every 3 years in patients with no risk factors to detect metachronous cancer at its curable stage. Because the gastric remnant after distal gastrectomy for synchronous multiple cancers did not show significantly higher risk for metachronous cancer than that seen after solitary cancer surgery in this study, we think this patient subset can follow our previous recommendations. In conclusion, the incidence of metachronous cancer in the gastric remnant is higher after multiple cancer surgery; however, the difference is not statistically significant.

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Conflict of interest This article has no potential or real conflicts of interest.

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胃癌ESD後穿孔に対して腹腔鏡下修復術が有用であった1例

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症例報告

胃癌ESD後穿孔に対して腹腔鏡下修復術が有用であった1例

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内容要旨

早期胃癌に対し, 内視鏡的粘膜下層剝離術(以下, ESD)は, 機能温存, 低侵襲の利点から広く行われているが, 合併症として穿孔が挙げられる. また, 消化器外科領域において手術侵襲軽減のため腹腔鏡下手術が広く施行されるようになってきている. 今回われわれは, 胃ESD後に合併した穿孔性腹膜炎に対し, 腹腔鏡下手術を施行し, 良好な経過をたどった1例を経験したので報告する.

症例は80歳の男性. 胃体上中部の早期胃癌に対してESDが施行された. ESD時に穿孔しクリップにて閉鎖したが, 16時間後に汎発性腹膜炎を合併し, 緊急手術を行った. 腹腔鏡下に縫合閉鎖による穿孔部の修復術およびドレナージ術を施行し, 術後は良好に経過した. 胃ESD後の穿孔性腹膜炎に対する腹腔鏡下修復術は, 有用な治療選択肢の一つと考えられた.

索引用語:内視鏡的粘膜下層剝離術, 胃穿孔, 腹腔鏡下手術

はじめに

近年, 早期胃癌に対し内視鏡的粘膜下層剝離術(ESD:Endoscopic Submucosal Dissection)が広く行われているが, 合併症の一つとして穿孔がある. 穿孔に対しては, クリップなどによる内視鏡的一期的閉鎖にて保存的治療が行われるが, 中には外科的治療を要する症例も存在する. 一方, 消化器外科領域において, 腹腔鏡手術が広く導入されるようになり, 術後早期回復などの有用性が報告されている. 今回われわれは, 胃ESD後に合併した穿孔性腹膜炎に対し腹腔鏡下修復術が有用であった1例を経験したので報告する.

症 例

患 者:80歳, 男性.

主 訴:検診発見.

家族歴:特記すべきことなし.

既往歴:急性虫垂炎にて虫垂切除術, 胆石症にて腹腔鏡下胆嚢摘出術.

現病歴:検診目的の上部消化管内視鏡検査にて, 胃体上中部小彎前壁に0-Ⅱc型胃癌を認め, 精査加療目的に消化器内科紹介となった.

現 症:腹部触診上異常なく, 表在リンパ節も触知しなかった.

入院時所見:血液生化学検査にてHb 11.7g/dlと軽度の貧血を認めたが, 他の検査所見は腫瘍マーカー(CEA, CA19-9)を含め基準範囲内であった. 心電図検査, 呼吸機能検査にも異常を認めなかった.

上部消化管内視鏡検査所見:胃体上中部小彎前壁に30mm大の浅い陥凹性病変を認め, 生検にて高分化管状腺癌と診断された(**Fig. 1a**). リンパ節・遠隔転移を認めず, 臨床診断:tub1, T1a (M) N0M0 Stage IAにて, 内視鏡的粘膜下層剝離術(ESD)の適応と考えられた.

ESD所見:胃体上部小彎~前壁の30mmの0-Ⅱc型早期胃癌に対してESDを施行した(**Fig. 1b**). ESD施行中に穿孔をきたし, クリップによる縫縮

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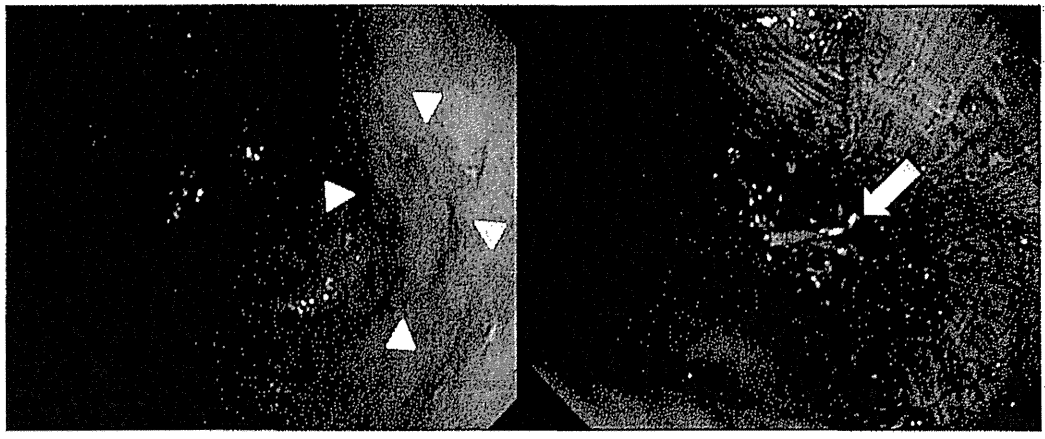

Fig. 1 a: Gastro-intestinal fiberscope revealed type 0-IIc gastric cancer in the upper to middle gastric body (short arrow).
b: The lesion was resected by ESD technique and perforated site was closed by metal clips during ESD (long arrow). a|b

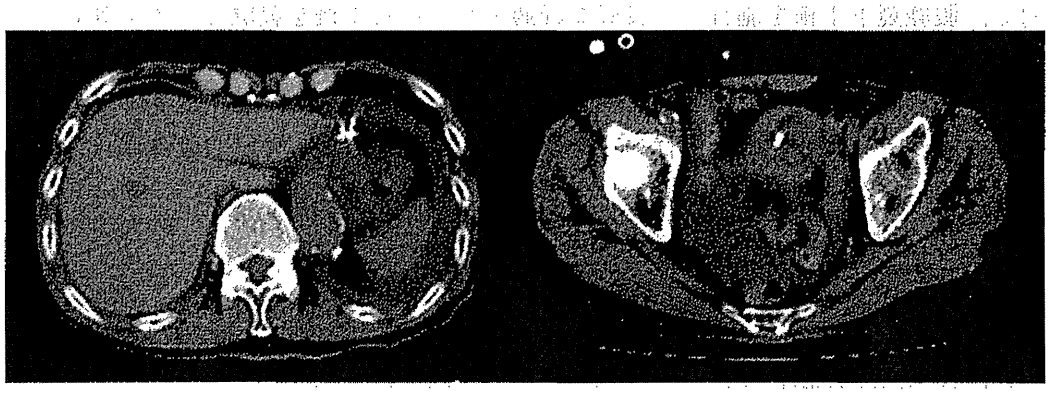

Fig. 2 Abdominal CT demonstrated free air and fluid collection in the abdominal cavity 16 hours after ESD. a|b

を要したが，病変は一括切除された．

ESD後経過：ESD施行後より，左上腹部の圧痛を認めたため，ESDから2時間後に腹部CTを施行した．CTでは，ESD穿孔時のものと考えられたフリーエアーと胃周囲の少量の体液貯留を認めたが，バイタルサインに著変なく，圧痛の部位も上腹部に限局していたため，保存的に加療する方針とした．絶飲食の上，経鼻胃管を挿入し胃内減圧を行い，プロトンポンプ阻害剤を使用しつつ，厳重に経過観察を行った．

その後，経過とともに38度を超える発熱と腹痛の増強を認めたため，ESD施行16時間後に再びCTを施行した．再CTにおいて，ESDより2時間後のCTと比較して腹腔内の液体貯留は明らかに増加し，ダグラス窩を含む腹腔内全体に広がっていた（**Fig. 2a, b**）．また，腹腔内のフリーエアーも増加しており，汎発性腹膜炎の診断にて外科紹介となった．腹部所見は，腹部全体に圧痛を認め，ESD2時間後の所見と比較して，明らかに圧痛を認める範囲が広がっていた．また，腹部全体でディフェンスあり，Blumbergサインも陽性であった．また，血液検査所見ではWBC 21,150/mm^3，CRP 7.58 mg/dlと炎症反応の増悪を認めた．以上より，ESD部の穿孔が原因と考えられる汎発性腹膜炎の診断にて，外科的処置が必要と判断し，緊急手術を施行した．

手術所見：胃癌病変はESDにて遺残なく一括切除されており，ESD前の深達度診断から今後リンパ節郭清を伴う胃切除は不要である可能性が極めて高いと考えられた．また，全身状態は保たれていたため，まず腹腔鏡を用いて腹腔内を観察する方針とした．臍部より12mmトラカールを挿入し，

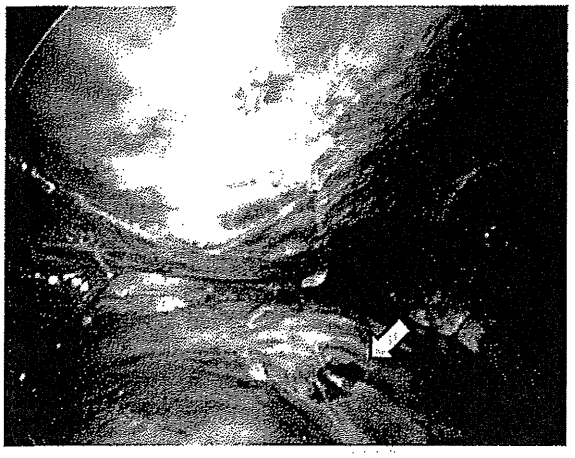

Fig. 3 Laparoscopic examination revealed the perforation site in the upper to middle gastric body (arrow).

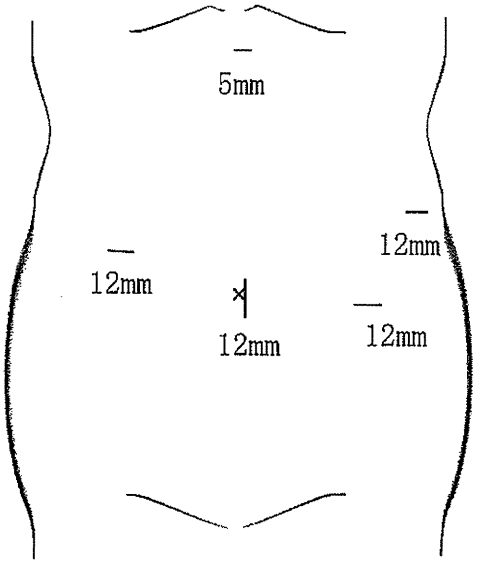

Fig. 4 Position of trocar sites in the laparoscopic repair.

8 cm H_2Oにて気腹し腹腔鏡にて腹腔内を観察した．胆汁を混じた胃液が腹腔内全体に広がっていた．胃上中部ESD施行部の胃壁は非薄化しており，その中央に穿孔を認めた（**Fig. 3**）．穿孔の原因は穿孔部を閉鎖していたクリップが外れたためと考えられた．**Fig. 4**のごとくトラカールを挿入した後に，まず温生食にて可及的に腹腔内を洗浄した．次いで穿孔部の処置へと移った．穿孔部周囲の胃壁は，ESDの剝離に伴い菲薄化しており，特に，穿孔部の胃壁は非常に脆弱であった．穿孔部のみの縫合では，容易に胃壁の二次的損傷をきたす恐れがあったため，次のような手順で縫合閉鎖を行った．まず穿孔部から離れて，ESD剝離肛門側端にあたる健常な胃壁のある体中下部小彎前壁に3-0 PDS®針を用いて全層1層縫合を行い，この糸を足側へ牽引用に利用した．この縫合から穿孔部のある噴門側へ向けて，3-0 PDS®にて順に全層1層縫合をかけてゆき穿孔部周囲の組織の緊張をとるようにしていった（**Fig. 5a**）．穿孔部の縫合は，特にバイトを大きめにとるように胃壁にかける運針を行い，一部小彎側の脂肪織とともに3-0 PDS®にて全層1層縫合を行い閉鎖した（**Fig. 5b**）．最終的に，7針の縫合により縫合閉鎖処置を行った（**Fig. 5c**）．さらに縫合閉鎖部を大網にて被覆し，3-0 PDS®による縫合で大網を胃壁に固定した後に，再び温生食にて腹腔内を十分に洗浄した．リークテストを施行し縫合閉鎖を確認したのちに，トラカール挿入部から横隔膜下およびダグラス窩にドレーンを挿入して手術を終了した．

術後経過：術後経過は良好であった．術後5日目に上部消化管内視鏡検査にて縫合部閉鎖を確認したのち，術後6日目より経口摂取を開始した．術後14日目には退院可能な状態となり，術後21日目に軽快退院となった．ESDによる摘出標本の病理結果は，30×22mm，well differentiated tubular adenocarcinoma (tub1>tub2)，pT1a (M)，ly0，v0，pHM（−），pVM（−），UL（−）であり，胃癌治療ガイドラインにおける適応拡大治癒切除と診断された．現在，外来通院で経過観察中であるが良好に経過し，術後9カ月の上部消化管内視鏡検査にて縫合閉鎖部の治癒を確認している（**Fig. 6**）．また2年3カ月間再発を認めていない．

考　察

近年，内視鏡技術の向上や，各種デバイスなどの開発により内視鏡治療の適応は広がりつつあり，早期胃癌に対するendscopic mucosal resection（以下，EMR）やESDの治療成績は広く認められるようになってきた[1)~7)]．EMRに比べ，ESDは粘膜を切開し粘膜下層を剝離することで，大きな一括切除が可能であり，また潰瘍瘢痕を有する病変でも切除が可能と報告され，癌遺残や局所再発の可能性を低減させるといわれている[2)~7)]．反面，高度の内視鏡技術が要求され，合併症が問題となる．合併症として問題となるのは，出血と穿孔であり，