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ORIGINAL ARTICLE

Combination chemotherapy with S-1 plus cisplatin for gastric cancer that recurs after adjuvant chemotherapy with S-1: multi-institutional retrospective analysis

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Abstract
Background It is unclear whether S-1 plus cisplatin is effective for patients with recurrent gastric cancer after adjuvant S-1 chemotherapy.
Methods We retrospectively evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant S-1 chemotherapy.
Results In the 52 patients evaluated, the median duration of adjuvant S-1 chemotherapy was 8.1 months, and the median recurrence-free interval (RFI) since the last administration of adjuvant S-1 was 6.4 months. Among the 36 patients with measurable lesions, 7 achieved a complete or partial response, and 13 were evaluated as having stable

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disease, for an overall response rate of 19.4% and a disease control rate of 55.6%. For all patients, the median progression-free survival (PFS) was 4.8 months, and the median overall survival (OS) was 12.2 months. Compared with patients with an RFI of <6 months ($n = 25$), patients with an RFI of ≥6 months ($n = 27$) had a significantly higher response rate (5.0 vs. 37.5%, respectively), longer PFS (2.3 vs. 6.2 months, respectively), and longer overall survival (7.3 vs. 16.6 months, respectively). According to a multivariate Cox model including performance status (PS) and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS and OS. *Conclusions* S-1 plus cisplatin is effective for patients with gastric cancer that recurs after adjuvant S-1 chemotherapy, especially for those with an RFI of ≥6 months.

Keywords Adjuvant chemotherapy · Gastric cancer · Recurrence · S-1

Introduction

Gastric cancer is the fourth most common malignancy in the world (988,602 cases in 2008, 7.8% of total malignancy cases) and the second leading cause of cancer death (737,419 deaths, 9.7% of total) [1]. The prognosis of patients with advanced or recurrent gastric cancer remains poor; chemotherapy confers only a minimal survival advantage, with a median survival of approximately 1 year. The most commonly used regimens are combination chemotherapy consisting of a fluoropyrimidine [5-fluorouracil (5-FU) or oral fluoropyrimidine] plus a platinum agent with or without docetaxel or anthracyclines [2–6].

S-1 is an oral anticancer drug composed of the 5-FU prodrug tegafur and two 5-FU modulators; it has achieved high response rates in patients with gastric cancer in phase II studies [7, 8]. In the Japan Clinical Oncology Group (JCOG) 9912 trial, which compared S-1, cisplatin plus irinotecan, and 5-FU, S-1 demonstrated non-inferiority compared to 5-FU [9]. In another phase III trial that compared S-1 alone to S-1 plus cisplatin (SPIRITS trial), S-1 plus cisplatin showed a significantly higher response rate (54 vs. 31%), longer progression-free survival (PFS; 6.0 vs. 4.0 months), and longer overall survival (OS; 13 vs. 11 months) [4]. Also, in a large, non-Japanese, phase III trial (the First-Line Advanced Gastric Cancer Study; FLAGS trial), S-1 plus cisplatin was associated with fewer toxic effects and demonstrated non-inferiority compared with 5-FU plus cisplatin by exploratory analysis [6]. Therefore, S-1 plus cisplatin is now considered to be one of the standard regimens for metastatic or recurrent gastric cancer.

In addition, the ACTS-GC trial has demonstrated that S-1 is also effective as adjuvant chemotherapy for Japanese patients who have undergone curative gastrectomy for locally advanced gastric cancer [10]. However, approximately 30% of patients still develop recurrence after curative resection followed by adjuvant S-1 [10]. As few patients who received adjuvant chemotherapy were included in the phase III trials described above [4, 7, 9], it is unclear whether patients who develop recurrence after adjuvant S-1 could achieve efficacy with S-1 plus cisplatin similar to that achieved in patients without adjuvant chemotherapy. To address this issue, we conducted the following multi-institutional retrospective analysis.

Patients and methods

Patients

This retrospective study was designed to evaluate the efficacy of first-line chemotherapy with S-1 plus cisplatin for recurrence in patients with gastric cancer who had undergone curative gastrectomy followed by adjuvant S-1 chemotherapy. Patients with histopathologically proven recurrent gastric adenocarcinoma after gastrectomy and lymph node dissection with no residual tumor were eligible for analysis. Additional eligibility criteria were: (1) previous adjuvant S-1 chemotherapy at a planned standard dose and schedule (80 mg/m^2 for 28 consecutive days followed by a 14-day rest; 42-day cycles to be repeated for 1 year); (2) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (3) adequate bone marrow, hepatic, and renal function to be treated with S-1 plus cisplatin; (4) evaluable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.1); and (5) treated with a standard regimen of S-1 plus cisplatin (S-1 80 mg/m^2 for 21 consecutive days followed by a 14-day rest; cisplatin 60 mg/m^2 intravenous infusion on day 8; 35-day cycles to be repeated) [4]. Written informed consent for treatment was obtained from each patient prior to treatment initiation. The Institutional Review Board of each participating center approved the study.

Evaluation of treatment and statistical analysis

The tumor response was assessed objectively according to RECIST ver. 1.1, and the best overall response was recorded as the antitumor effect for that patient. The disease control rate (DCR) represented the percentage of patients with a complete response (CR), partial response (PR), or stable disease (SD). PFS was measured from the date of initiation of S-1 plus cisplatin to the date of progressive disease or death from any cause. Time to treatment failure

(TTF) was measured from the date of initiation of S-1 plus cisplatin to the date of last administration of S-1. OS was estimated from the date of initiation of S-1 plus cisplatin to the date of death or last follow-up visit, using the Kaplan–Meier method. The interval from the last administration of adjuvant S-1 to recurrence was defined as the recurrence-free interval (RFI).

The Cox proportional hazards model was used to estimate the impact of the RFI on TTF, PFS, and OS, with adjustment for other factors that were shown to be significant with a univariate log-rank test. *P* values for testing differences between proportions and response rates were calculated with χ^2 tests for homogeneity or for trend, or with Fisher's exact test. Results were considered to be statistically significant when the *P* value was <0.05. All reported *P* values are two-sided. In particular, we compared the response rate, DCR, time to progression (TTP), PFS, and OS between patients with RFIs of ≥6 and <6 months, because several clinical trials in the first-line setting set this interval of ≥6 months as an inclusion criterion [5, 9, 11].

Results

Patient characteristics

A total of 406 patients with recurrent gastric cancer after adjuvant S-1 chemotherapy had received chemotherapy at 18 institutions until October 2010. Among them, 57 patients (14.0%) had received S-1 plus cisplatin as first-line chemotherapy for recurrence. After the exclusion of 5 patients (1 patient with a non-evaluable lesion and 4 patients with insufficient data), 52 patients were included in the final

Table 1 Patient characteristics

Characteristic	All ($n = 52$)	RFI <6 months ($n = 25$)	RFI ≥6 months ($n = 27$)	*P* value
Age, years				
Median (range)	61 (32–77)	59 (32–77)	62 (32–77)	
Gender, *n* (%)				
Male	30 (58)	15 (60)	15 (56)	0.75
Female	22 (42)	10 (40)	12 (44)	
ECOG PS at recurrence, *n* (%)				
0	32 (62)	11 (44)	21 (78)	*0.012*
1	20 (38)	14 (56)	6 (22)	
Histological type[a], *n* (%)				
wel or mod	27 (52)	10 (40)	17 (63)	0.1
por or sig	24 (46)	15 (60)	9 (33)	
Other	1 (2)	–	1 (4)	
Pathological stage[a], *n* (%)				
Stage I or II	8 (15)	4 (16)	4 (15)	0.57
Stage IIIA	17 (33)	6 (24)	11 (41)	
Stage IIIB	15 (29)	8 (32)	7 (26)	
Stage IV	12 (23)	7 (28)	5 (19)	
Site of recurrence, *n* (%)				
Peritoneum	21 (40)	7 (28)	14 (52)	0.08
Lymph node	25 (48)	13 (52)	12 (44)	0.59
Liver	14 (27)	10 (40)	4 (15)	*0.041*
Lung	4 (8)	3 (12)	1 (4)	0.262
Bone	6 (12)	1 (4)	5 (19)	0.102
Local	2 (4)	1 (4)	1 (4)	0.96
Number of recurrence sites, *n* (%)				
1	38 (73)	18 (72)	20 (74)	0.87
2 or more	14 (27)	7 (28)	7 (26)	

P values shown in italics indicate significant differences

RFI Recurrence-free interval, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group, *wel* well-differentiated adenocarcinoma, *mod* moderately differentiated adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring-cell-like carcinoma

[a] According to the Japanese classification

analysis (Table 1). The median duration of adjuvant S-1 chemotherapy was 8.1 months (range 0.7–37.4 months), and the median RFI since the last administration of adjuvant S-1 was 6.4 months (range 0–81.3 months). Thirty of the 52 patients (57.7%) completed the planned duration of adjuvant S-1 therapy. In contrast, 14 patients discontinued S-1 due to disease recurrence, and 8 patients stopped therapy due to toxicity or patient refusal. Other than PS and liver metastasis, characteristics did not differ significantly between patients with an RFI of ≥6 months ($n = 27$) and those with an RFI of <6 months ($n = 25$) (Table 1).

Treatment results and efficacy

The median TTF was 4.1 months (95% confidence interval [CI] 2.5–5.1 months), with a median duration of follow-up of 32 months. Forty-four patients discontinued S-1 plus cisplatin due to disease progression ($n = 40$, 90.9%) or toxicity ($n = 4$, 9.1%). Of the 36 patients with measurable lesions, 7 achieved a CR ($n = 3$) or a PR ($n = 4$), and 13 were evaluated as having SD, for an overall response rate of 19.4% (95% CI 7.0–37.0%) and a DCR of 55.6% (95% CI 38.1–72.1%). The median PFS was 4.8 months (95% CI 3.9–6.2 months), and the median OS of all patients was 12.2 months (95% CI 10.2–16.6 months) (Fig. 1). Of the 44 patients who had discontinued S-1 plus cisplatin, 31 (70.4%) received second-line or third-line chemotherapy, including taxanes ($n = 25$) or irinotecan ($n = 17$).

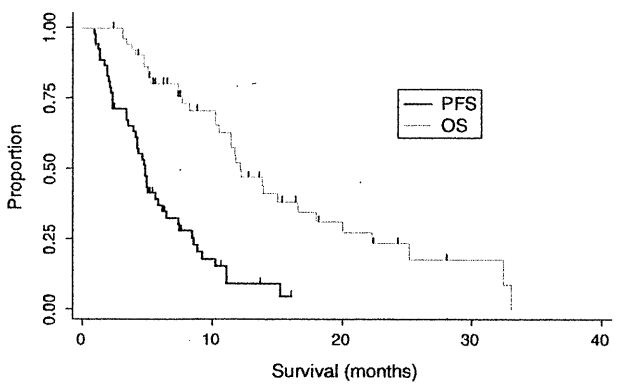

Fig. 1 Progression-free survival (*PFS*) and overall survival (*OS*) in all patients. The median PFS was 4.8 months (95% confidence interval [CI] 3.9–6.2 months), and the median OS was 12.2 months (95% CI 10.2–16.6 months). *PFS* progression-free survival, *OS* overall survival

Significance of the RFI

The response rate was significantly better in patients with an RFI of ≥6 months (37.5%; 95% CI 14–61%) than that in patients with an RFI of <6 months (5.0%; 95% CI 0–15%, $P = 0.014$, Table 2). In addition, compared with patients with an RFI of <6 months, patients with an RFI of ≥6 months had a significantly longer TTF (2.5 vs. 5.1 months, respectively, $P = 0.025$), longer PFS (2.3 vs. 6.2 months, respectively, $P < 0.001$, Fig. 2), and longer OS (7.3 vs. 16.6 months, respectively, $P = 0.003$, Fig. 2). According to a multivariate Cox model including PS and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS (hazard ratio [HR] 0.35, 95% CI 0.16–0.77, $P = 0.009$) and OS (HR 0.21, 95% CI 0.08–0.54, $P = 0.001$), although the association with TTF was not significant (HR 0.55, 95% CI 0.27–1.12, $P = 0.1$). When we divided the patients into two groups based on an RFI of 12 months, no significant difference between the groups was found in response rate, TTP, PFS, or OS.

Discussion

In the ACTS-GC study, adjuvant S-1 chemotherapy significantly improved the survival of patients who had undergone curative gastrectomy for locally advanced gastric cancer [10]. On the other hand, several small studies have suggested that patients with recurrence after adjuvant S-1 were refractory to S-1-containing regimens or had a worse prognosis compared with that of patients without adjuvant chemotherapy [12–14]. Although these reports never precluded the use of adjuvant S-1 chemotherapy, they raised the issue of how to treat recurrent disease after adjuvant S-1.

In the present retrospective study, we evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant chemotherapy with S-1. The response rate of 19.4% and PFS of 4.8 months were

Table 2 Objective response rates in patients with measurable lesions

	n	CR	PR	SD	PD	NE	ORR (%)	95% CI (%)
All	36	3	4	13	14	2	18.8	7–32
RFI <6 months	20	0	1	6	13	0	5.0	0–15
RFI ≥6 months	16	3	3	7	1	2	37.5	14–61

CR Complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* objective response rate, *CI* confidence interval

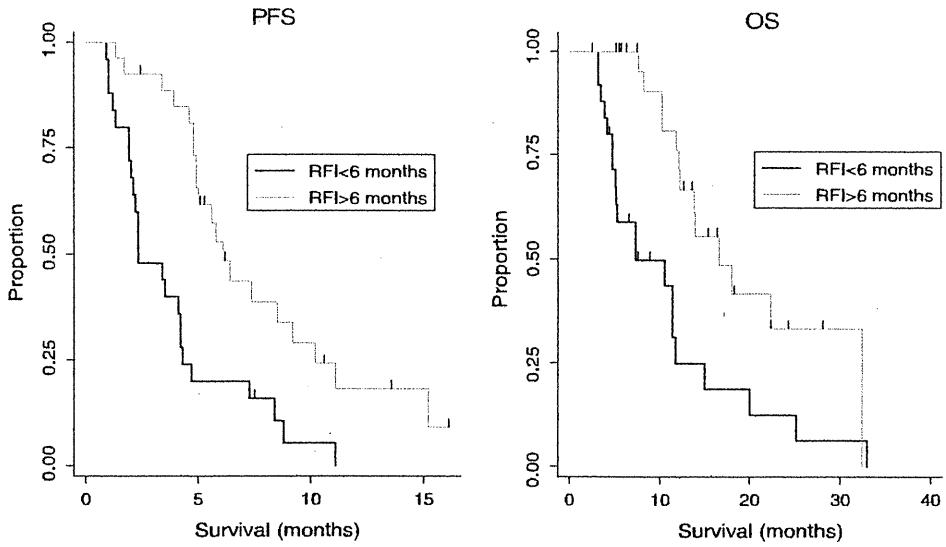

Fig. 2 Progression-free survival (*PFS*) and overall survival (*OS*) according to the length of the recurrence-free interval (*RFI*). Patients with an RFI of ≥6 months had a significantly longer median PFS (6.2 vs. 2.3 months, $P < 0.001$) and OS (16.6 vs. 7.3 months, $P = 0.003$) than patients with an RFI of <6 months. *RFI* recurrence-free interval, PFS progression-free survival, OS overall survival

relatively worse compared with those in the SPIRITS study [4]. However, our results also suggested that patients with an RFI of ≥6 months who received S-1 plus cisplatin had a significantly better response rate, longer PFS, and longer OS compared to patients with an RFI of <6 months. The efficacy of S-1 plus cisplatin for patients with an RFI of ≥6 months in this study was almost compatible with that of patients in the SPIRITS trial in terms of PFS and OS, although these results should be interpreted cautiously due to the heterogeneity of the characteristics of the patients in the two studies. Although no prospective study has evaluated any chemotherapy specifically for patients who have failed adjuvant S-1, Kang and colleagues [15] conducted a phase II study of capecitabine plus cisplatin for 32 patients with gastric cancer that recurred after adjuvant chemotherapy with doxifluridine or 5-FU-containing regimens. They reported a response rate of 28% and a median TTP of 5.8 months, and concluded that capecitabine plus cisplatin was effective as first-line treatment in patients with recurrent gastric cancer after fluoropyrimidine-based adjuvant chemotherapy. In their report, the response rates (21 vs. 39%, $P = 0.427$), TTF (8.3 vs. 5.4 months, $P = 0.072$), and OS (14.1 vs. 9.3 months, $P = 0.075$) tended to be better in patients with an RFI of >6 months ($n = 13$) than in patients with an RFI of ≤6 months ($n = 19$), although the differences did not reach statistical significance [15]. These results were also consistent with those of previous studies in patients with other types of cancer, which suggested the importance of the RFI or treatment-free interval as a predictive marker of responsiveness to similar types of chemotherapy after recurrence [16–18]. Additionally, in the present study, the RFI cut-off value of 6 months was better than that of 12 months for predicting better outcomes and this finding may support the use of the conventional exclusion criteria in clinical trials in the first-line setting, which excluded patients who experienced disease recurrence within 6 months after the last adjuvant chemotherapy [5, 9, 11]. Therefore, selected patients with an RFI of ≥6 months with sufficient organ function may be adequately treated as chemo-naïve patients with standard chemotherapies such as S-1 plus cisplatin.

In contrast to the results for patients with an RFI of ≥6 months, the response rate in patients with an RFI of <6 months in the present study seemed to be worse than that of commonly used second-line chemotherapy regimens such as irinotecan and taxane combinations, which have a reported response rate of approximately 20% for patients with gastric cancer who received prior chemotherapy with fluoropyrimidines alone [18–23]. Based on these results, it may be suggested that the evaluation of chemotherapy regimens other than S-1 plus cisplatin might be warranted for the initial treatment of gastric cancer recurrence after adjuvant S-1. The response rate of 5.0% in our subset of patients with an RFI of <6 months was also lower than that reported previously by Kang et al. for capecitabine plus cisplatin after adjuvant chemotherapy (21%) [15]. The exact reasons for this difference are unknown. One possible reason is that Kang and colleagues did not use the same fluoropyrimidine (capecitabine after doxifluridine or 5-FU), and this choice might have contributed to a higher response in regard to early recurrence, although rechallenge with different types of fluoropyrimidine after the failure of another drug is still controversial in several types of cancer [24–28]. Second, the planned dose intensity of cisplatin as another key drug for gastric cancer was higher in their capecitabine plus cisplatin regimen (60 mg/m^2 every 3 weeks) [15] than that in the S-1 plus cisplatin regimen (60 mg/m^2 every 5 weeks). The efficacy of capecitabine plus cisplatin compared with other

chemotherapy (irinotecan, taxane or irinotecan plus cisplatin) for recurrence after adjuvant S-1 should be evaluated in future clinical trials.

It is important to note the limitations of the present study. First, it was retrospective, and treatment after recurrence was selected by each physician individually. Considering the low proportion of patients who received S-1 plus cisplatin after recurrence (14.0%), the selected population may have been biased toward patients with good performance status (PS) and low tumor burden. Second, toxicity was not evaluated in this study, although the proportion of patients who discontinued S-1 plus cisplatin due to toxicity was low. Third, human epidermal growth factor receptor 2 (HER2) status was not evaluated. Trastuzumab, a humanized monoclonal antibody against HER2, has recently been shown to improve the prognosis of HER2-positive advanced gastric cancer [29]; and the HER2 status of all gastric cancer types should be evaluated, even in this setting of recurrent disease. Fourth, the moderate sample size in a single-country study is another limitation; therefore, it would be better to validate the significance of the RFI after adjuvant failure on the PFS in other cohorts as well.

In conclusion, this is the first report to have evaluated the efficacy of chemotherapy with S-1 plus cisplatin in patients with gastric cancer that recurred after adjuvant chemotherapy with S-1. S-1 plus cisplatin was effective in such patients, especially in those with an RFI of $\geq$6 months. Further well-defined, prospective trials in this important patient population are required to identify optimal treatment regimens.

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Conflict of interest None of the authors have financial or personal conflicts of interest to disclose.

References

1. International Agency for Research on Cancer. GLOBOCAN. http://www-dep.iarc.fr/CancerMondial.htm (2008). Accessed April 2011
2. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006;24:4991–7.
3. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36–46.
4. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
5. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol. 2009;20:666–73.
6. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28:1547–53.
7. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer. 1998;34:1715–20.
8. Koizumi W, Kurihara M, Nakano S, Hasegawa K. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. Oncology. 2000;58:191–7.
9. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol. 2009;10:1063–9.
10. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810–20.
11. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study. J Clin Oncol. 2011 Aug 15. [Epub ahead of print]
12. Shitara K, Muro K, Ura T, Takahari D, Yokota T, Sawaki A, et al. Chemotherapy for gastric cancer that recurs after adjuvant chemotherapy with S-1. Jpn J Clin Oncol. 2008;38:786–9.
13. Hasegawa H, Fujitani K, Kurokawa Y, Hirao M, Nakazuru S, Mita E, et al. Effect of S-1 adjuvant chemotherapy on survival following recurrence and efficacy of first-line treatment in recurrent gastric cancer. Chemotherapy. 2010;56:436–43.
14. Aoyama T, Yoshikawa T, Watanabe T, Hayashi T, Ogata T, Cho H, et al. Survival and prognosticators of gastric cancer that recurs after adjuvant chemotherapy with S-1. Gastric Cancer. 2011;14:150–4.
15. Kang HJ, Chang HM, Kim TW, Ryu MH, Sohn HJ, Yook JH, et al. Phase II study of capecitabine and cisplatin as first-line combination therapy in patients with gastric cancer recurrent after fluoropyrimidine-based adjuvant chemotherapy. Br J Cancer. 2005;92:246–51.
16. Pujade-Lauraine E, Paraiso D, Cure H, Germann N, Lortholary A, Lucas V, et al. Predicting the effectiveness of chemotherapy (Cx) in patients with recurrent ovarian cancer (ROC): a GINECO study. Proc Am Soc Clin Oncol 2002;21:abstract 829.
17. Takashima A, Shirao K, Hirashima Y, Takahari D, Okita N, Akatsuka S, et al. Chemosensitivity of patients with recurrent esophageal cancer receiving perioperative chemotherapy. Dis Esophagus. 2008;21:607–11.
18. de Gramont Lesparre AH, Chibaudel B, Bourges O, Perez-Staub N, Tournigand C, Maindrault-Goebel F, et al. Definition of oxaliplatin sensitivity in patients with advanced colorectal cancer previously treated with oxaliplatin-based therapy. J Clin Oncol. 2009;27:15s. (abstr 4024).
19. Futatsuki K, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, et al. Late phase II study of irinotecan hydrochloride (CPT-11) in

advanced gastric cancer. CPT-11 Gastrointestinal Cancer Study Group. Gan To Kagaku Ryoho. 1994;21:1033–8.
20. Taguchi T, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, et al. Late phase II clinical study of RP56976 (docetaxel) in patients with advanced/recurrent gastric cancer: a Japanese Cooperative Study Group trial (group A). Gan To Kagaku Ryoho. 1998;25:1915–24.
21. Mai M, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, et al. A late phase II clinical study of RP56976 (docetaxel) in patients with advanced or recurrent gastric cancer: a Cooperative Study Group Trial (group B). Gan To Kagaku Ryoho. 1999;26:487–96.
22. Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, et al. Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol. 2001;12:1133–7.
23. Nakae S, Hirao M, Kishimoto T, Iijima S, Ishida H, Morimoto T, et al. Phase II study of bi-weekly CPT-11 + CDDP for patients with gastric cancer refractory to S-1 (OGSG 0504 study). J Clin Oncol 2008;26 (May 20 suppl; abstr 4571).
24. Lee JJ, Kim TM, Yu SJ, Kim DW, Joh YH, Oh DY, et al. Single-agent capecitabine in patients with metastatic colorectal cancer refractory to 5-fluorouracil/leucovorin chemotherapy. Jpn J Clin Oncol. 2004;34:400–4.
25. Yasui H, Yoshino T, Boku N, Onozawa Y, Hironaka S, Fukutomi A, et al. Retrospective analysis of S-1 monotherapy in patients with metastatic colorectal cancer after failure to fluoropyrimidine and irinotecan or to fluoropyrimidine, irinotecan and oxaliplatin. Jpn J Clin Oncol. 2009;39:315–20.
26. Takiuchi H, Goto M, Imamura H, Furukawa H, Imano M, Imamoto H, et al. Multi-center phase II study for combination therapy with paclitaxel/doxifluridine to treat advanced/recurrent gastric cancer showing resistance to S-1 (OGSG 0302). Jpn J Clin Oncol. 2008;38:176–81.
27. Ono A, Boku N, Onozawa Y, Hironaka S, Fukutomi A, Yasui H, et al. Activity of S-1 in advanced or recurrent gastric cancer patients after failure of prior chemotherapy, including irinotecan + cisplatin or fluorouracil (except S-1). Jpn J Clin Oncol. 2009;39:332–5.
28. Yamamoto D, Yoshida H, Iwase S, Odagiri H, Kitamura K. TS-1 in patients with capecitabine-resistant breast cancer. J Clin Oncol 27:15s, 2009 (suppl; abstr 1103).
29. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97.

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症　例

D3郭清により5年以上生存した多発大動脈周囲リンパ節転移を伴う高度進行胃癌の1例

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浦野真一　二宮基樹　西崎正彦　原野雅生

症例は50代，男性．糖尿病加療中であったが，体重減少を主訴に近医受診精査の結果，胃癌と診断され当院に紹介された．上部消化管内視鏡検査で食道浸潤を認めるType3胃癌を認め，CTにて大動脈周囲リンパ節の累々とした腫脹を認め転移が疑われた．胃全摘，食道および横隔膜部分切除，脾摘，胆摘，D3郭清を施行し，術後病理診断にて総摘出リンパ節個数91個のうち22個に転移を認め，うち大動脈周囲リンパ節36個中11個に転移を認めた．術後7年経過した現在，自覚症状を特に認めずCTと内視鏡で再発所見を認めていない．実質的には十分な術後補助化学療法も施行せず，11個もの多発大動脈周囲リンパ節転移を呈しながら，大動脈周囲リンパ節郭清を伴う根治術により7年生存した例は稀であり若干の文献的考察を加えて報告する．

索引用語：大動脈周囲リンパ節転移，D3郭清，para-aortic lymph node dissection

緒　言

本邦における進行胃癌の標準郭清はD2郭清とガイドラインで定められている[1)2)]．他方，1976年に大動脈周囲リンパ節転移を伴う進行胃癌に対して大動脈周囲リンパ節郭清（以下D3郭清）施行例の5年生存例が報告され[3)]，その後も技術的蓄積が進み，D3郭清が積極的に行われるようになった[4)5)]．しかし，JCOG9501（大動脈周囲リンパ節郭清の臨床的意義に関する研究）の結果により切除可能な進行胃癌に対する予防的D3郭清の意義は否定され[6)]，その後この拡大手術手技は急速に行われなくなってきている．

しかし，大動脈周囲リンパ節転移陽性胃癌に対する治療的D3郭清の意義の検証はいまだになされていない．大動脈周囲リンパ節に11個もの転移を認め，術後に十分な補助化学療法を行えなかったにもかかわらずD3郭清により術後7年経った現在でも無再発生存している症例を経験したので報告する．

症　例

症例：50代，男性．

主訴：体重減少．

家族歴：母に胃癌の既往あり．

既往歴：糖尿病・高脂血症にて近医にて内服加療中．

現病歴：2003年3月より体重減少を自覚し，近医にて精査を行った．上部消化管造影，および内視鏡検査にて胃体上部から食道下部にまで拡がる腫瘍を認め，生検にて低分化型腺癌（por）と診断された．手術適応として当院紹介受診となり，2003年6月入院となった．

入院時現症：身長172cm，体重58kg．眼瞼，眼球結膜に貧血や黄疸なく頸部，腋窩リンパ節は触知しなかった．心肺に異常を認めず腹部は平坦で軟であった．

入院時検査成績：血液生化学検査にてHb 10.5g/dl，Hct 32.8%と軽度の貧血を認め，またHbA1c 7.6%と上昇していた．それ以外には特記すべき異常所見は認めず腫瘍マーカーの上昇も認めなかった．

上部消化管X線造影検査：胃大彎側，小彎側にそれぞれ壁不整を認めた．壁不整は食道下部まで進展し，食道胃接合部より3cmの食道浸潤が疑われた（**Fig. 1**）．

上部消化管内視鏡検査：胃体上部～体下部前壁にかけて易出血性のType3腫瘍を認め，生検にてGroup5，porと診断された．また食道胃接合部直上前壁に結節状隆起を認めた（**Fig. 2**）．

腹部CT検査：食道胃接合部に腫瘤を認め，胃体上部や腹腔動脈周囲根部に多数のリンパ節腫大を認め

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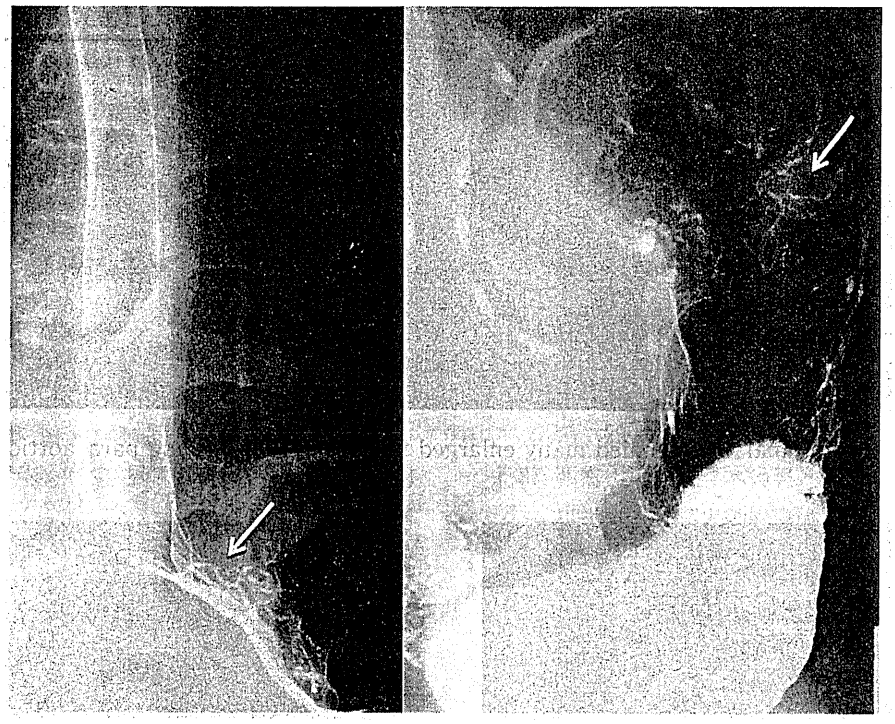

Fig. 1 Radiological examination showed a defect and an irregularity on the lesser and greater curvatures. Gastric cancer invaded the esophagus by 2-3cm.

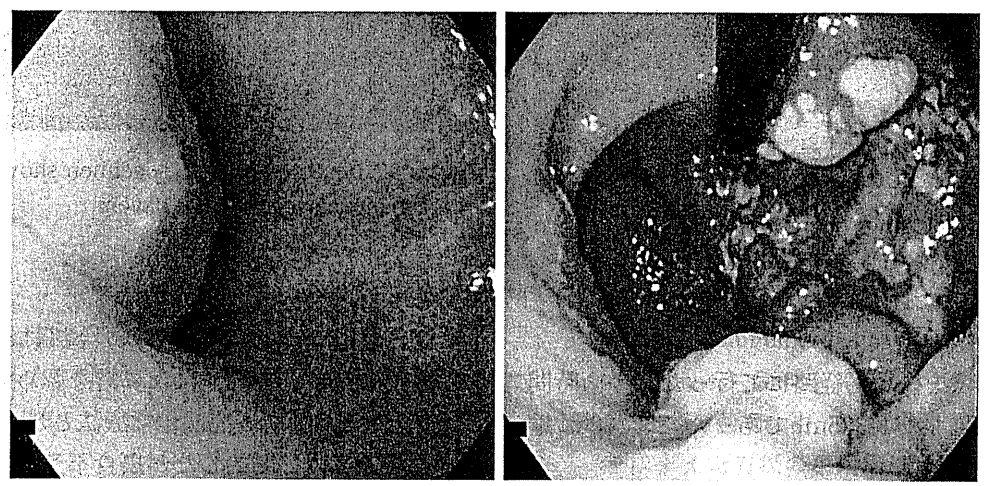

Fig. 2 Type3 advanced cancer located in the anterior wall of the upper part of the gastric body. Biopsy revealed poorly differentiated adenocarcinoma (*por*).

た．また，No.16blinter を中心とするリンパ節腫大を複数個認め，転移が疑われたが他臓器への遠隔転移は認めなかった（**Fig. 3**）．

手術：以上の所見から大動脈周囲リンパ節に転移を有する stage IV の Type3胃癌と診断し術前化学療法を行う方針としたが，患者本人の仕事の都合により困難であり2003年6月に手術を施行した．

手術所見で腹水はなく，Schnitzler 転移をはじめとする腹膜播腫も認めず，洗浄細胞診も陰性であったので，大動脈周囲リンパ節郭清（**Fig. 4**）を伴う胃全摘，脾摘，胆摘，横隔膜・食道部分切除を施行した．胃切離後食道近位断端を迅速病理に提出したところリンパ管侵襲陽性との診断にて食道追加切除を行い，その後の再迅速診断にて切離断端陰性との診断を得た．再建

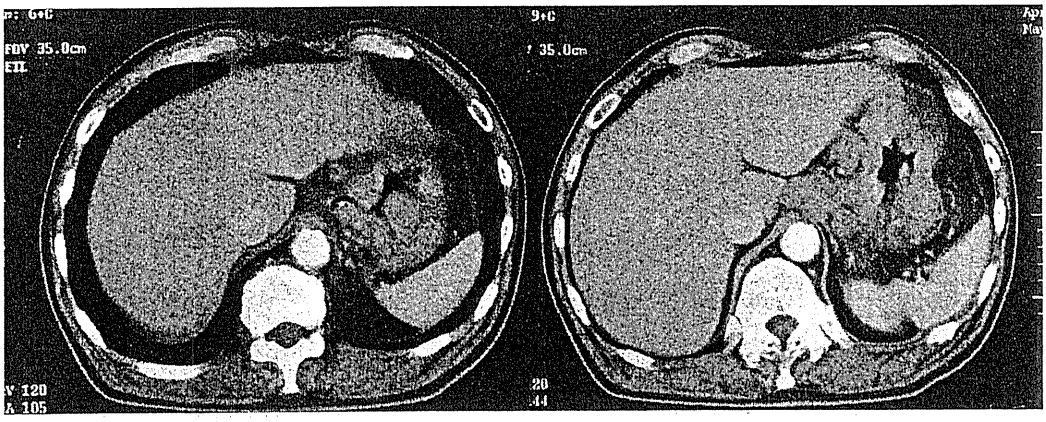

Fig. 3　Abdominal CT revealed many enlarged lymph nodes, including para-aortic nodes.

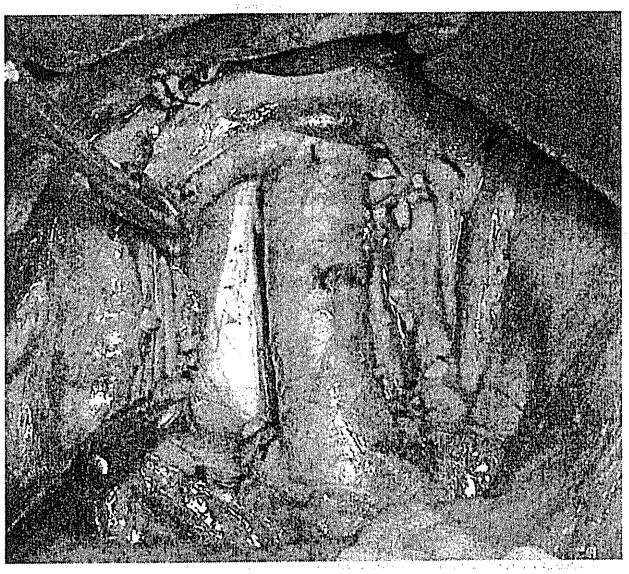

Fig. 4　Operative findings : The tumor was exposed to the serosa.

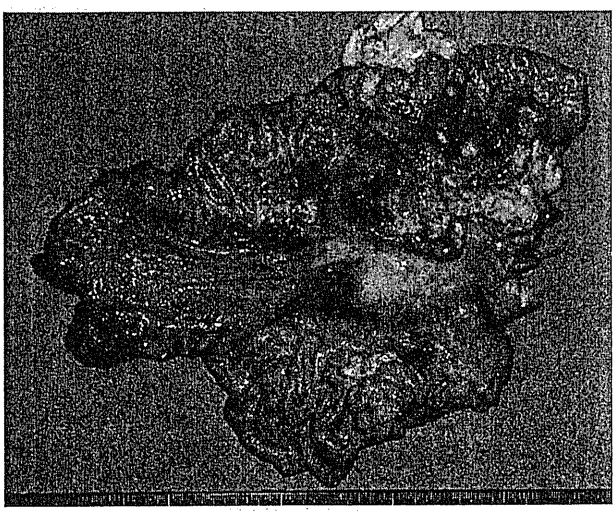

Fig. 5　Resected gastric specimen shows a type3 cancer measuring 6.5cm×10.0cm.

はRoux-en-Y法を後結腸経路にて行った．手術時間9時間31分で出血量が1,335mlであったため800ml輸血を行った．

術後病理組織学的所見：切除標本で胃体上部後壁を中心とした亜全周性の6.5cm×10.0cmの腫瘍を認めた（**Fig. 5**）．腫瘍は潰瘍浸潤型で壁進達度はSEであった．組織型はpor1を主体とし，tub2，por2の混在も認めた．INFβ，med，PM(−)，DM(−)で腫瘍はly3，v2と高度の脈管侵襲を認めた．総摘出リンパ節91個中22個に転移を認めた．内訳は1群に6/23(No.1，No.3，No.4sb)，2群に5/12 (No.7，No.8a，No.9)，そして大動脈周囲リンパ節転移は11/36に転移が認められ，それぞれの分布はNo.16a2inter：1/2，No.16a2latero：1/2，No.16b1inter：7/12，No.16b1latero：2/20であった．

術後経過：術後食道空腸吻合部にminor leakageをきたしたが，その他には異常を認めず術後34病日に退院となった．術後補助化学療法としてTS-1 100mg/日を4投2休で開始したが摂食不良，易疲労感などが強く術後約半年の服用にとどまり，以降は化学療法を行わなかった．術後半年目のCT検査で腹水を認め腹膜播種も疑われたが，その後自然に軽快し以降は再発所見を認めなかった．術後7年経過した現在，無再発生存中である．

考　察

進行胃癌におけるNo.16リンパ節転移頻度は20-35％とされており[7]，D3郭清を施行後の5年生存率は11-23％と報告されている[8]．しかしD3郭清を行い5年生存を果たせた症例は3個以下の転移がほとんどであり[9][10]，10個以上の転移がありながら5年生存してい

る症例は稀である[11)12)]．最近では化学療法の進歩にともない，No.16リンパ節転移があった場合でも術前化学療法，それに続く手術療法により良い成績をあげたとされた報告が数多く見られる[13)]．しかし，本症例では多数のNo.16リンパ節への転移を有し，また術後に十分な化学療法が行えなかったにもかかわらず術後7年無再発にて経過できたのはD3郭清が遂行できた結果と考えられる．JCOG9501によって予防的D3郭清は否定されたが，治療的D3郭清の意義もが否定されたわけではなく[14)]，本症例はその可能性を示すものである．D3郭清の適応はNo.16リンパ節への転移数が少なく根治度Bの手術が可能である症例との報告が一般的であるが[15)]，自験例はその基準からはずれていた．本症例はH0P0で原発巣，リンパ節の一括的切除が可能ならば，No.16リンパ節転移数が多数であれ手術による治癒の可能性を示唆している[16)]．No.16リンパ節転移を10個以上認め，D3郭清にて長期生存を得た症例は数例の報告を認めるだけであるが，D3郭清にて長期生存の得られる条件としてはP0，H0で原発病巣のコントロールが可能であり，根治度Bの手術が可能な症例には期待できると考える．大動脈周囲リンパ節への転移が多い現在報告されている症例について，長期生存が手術にて可能であった共通した条件は認めていない．しかし，化学療法が進歩した現在では術前化学療法後のD3郭清が現実的であり，術前化学療法が著効する症例については今後その可能性は広がると考える．同治療法は現在JCOG等で検証中であるが，その結果が待たれる．

結　語

11個もの大動脈周囲リンパ節への転移を認めながら，D 3郭清後に術後7年無再発生存中の症例を経験した．本例は治療的大動脈周囲郭清の意義を完全には否定できないことを示すものである．

文　献

1) 胃癌学会編：胃癌治療ガイドライン．2004年4月改訂第2版，金原出版，東京，2004
2) 胃癌学会編：胃癌取扱い規約．(第13版)，金原出版，東京，1999
3) 大橋一郎，高木國夫，小西敏郎他：胃癌の大動脈周囲リンパ節転移陽性の5年生存例について．日消外会誌　1976；9：112—116
4) 徳田　一，高橋　滋，竹中　温他：胃癌の超拡大郭清における適応とその限界．日外会誌　1988；89：1528—1530
5) 太田恵一朗，西　満正，大山繁和他：進行胃癌に対する腹部大動脈周囲リンパ節郭清の功罪．日消外会誌　1995；28：918—922
6) Sasako M, Sano T, Yamamoto S, et al : Japan Clinical Oncology Group. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 2008 ; 359 : 453—462
7) 高橋　滋：腹部大動脈周囲リンパ節郭清例からみた胃癌リンパ節転移の検討．日外会誌　1990；91：29—35
8) 梨本　篤，佐々木壽英，赤井貞彦：進行胃癌症例に対する腹部大動脈周囲リンパ節転移への主要リンパ経路および郭清の意義に関する検討．日消外会誌　1991；24：1169—1178
9) Yoshizumi Y, Matuyama T, Koike H, et al : Long-term survival after gastric cancer and liver and paraaortic lymph node metastases. Surg Today 2001 ; 31 : 159—162
10) Nashimoto A, Sasaki J, Sano M, et al : Disease-free survival for 6 years and 4 months after dissection of recurrent abdominal paraaortic nodes (No.16) in gastric cancer. Surg Today 1997 ; 27 : 169—173
11) 宗岡克樹，梨本　篤，佐々木壽英：腹部大動脈周囲リンパ節に26個転移を認め5年生存した進行胃癌の1例．日消外会誌　1995；28：1938—1942
12) Inada T, Ogata Y, Ozawa I, et al : Long-term postoperative survival of a gastric cancer patient with numerous para-aortic lymph node metastases. Gastric Cancer 1999 ; 2 : 235—239
13) 梨本　篤，藪崎　裕，中川　悟：JCOG9501の結果を踏まえた胃癌の手術治療．外科治療　2007；97：370—382
14) 梨本　篤，藪崎　裕，中川　悟：進行胃癌に対する拡大手術の適応と問題点—拡大リンパ節郭清と他臓器合併切除を中心に．外科　2006；68：1712—1717
15) 梨本　篤，藪崎　裕，中川　悟：特集　胃癌手術入門D3リンパ節郭清：適応と手技．手術　2008；62：573—577
16) 笹子三津留：胃癌に対するリンパ節郭清の治療的意義．外科治療　2007；96：834—836